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Beta-blockers for preventing aortic dissection in Marfan syndrome.
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[Intervention Review]

Beta-blockers for preventing aortic dissection in Marfan syndrome

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ABSTRACT

Background

Marfan syndrome is a hereditary disorder affecting the connective tissue and is caused by a mutation of the fibrillin-1 (FBN1) gene. It affects multiple systems of the body, most notably the cardiovascular, ocular, skeletal, dural and pulmonary systems. Aortic root dilatation is the most frequent cardiovascular manifestation and its complications, including aortic regurgitation, dissection and rupture are the main cause of morbidity and mortality.

Objectives

To assess the long-term efficacy and safety of beta-blocker therapy as compared to placebo, no treatment or surveillance only in people with Marfan syndrome.

Search methods

We searched the following databases on 28 June 2017; CENTRAL, MEDLINE, Embase, Science Citation Index Expanded and the Conference Proceeding Citation Index - Science in the Web of Science Core Collection. We also searched the Online Metabolic and Molecular Bases of Inherited Disease (OMMBID), ClinicalTrials.gov and the World Health Organization (WHO) International Clinical Trials Registry Platform (ICTRP) on 30 June 2017. We did not impose any restriction on language of publication.

Selection criteria

All randomised controlled trials (RCTs) of at least one year in duration assessing the effects of beta-blocker monotherapy compared with placebo, no treatment or surveillance only, in people of all ages with a confirmed diagnosis of Marfan syndrome were eligible for inclusion.

Data collection and analysis

Two review authors independently screened titles and abstracts for inclusion, extracted data and assessed trial quality. Trial authors were contacted to obtain missing data. Dichotomous outcomes will be reported as relative risk and continuous outcomes as mean differences with 95% confidence intervals. We assessed the quality of evidence using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach.

Main results

One open-label, randomised, single-centre trial including 70 participants with Marfan syndrome (aged 12 to 50 years old) met the inclusion criteria. Participants were randomly assigned to propranolol (N = 32) or no treatment (N = 38) for an average duration of 9.3 years in the control group and 10.7 years in the treatment group. The initial dose of propranolol was 10 mg four times daily and the optimal dose was reached when the heart rate remained below 100 beats per minute during exercise or the systolic time interval increased by 30%. The mean (± standard error (SE)) optimal dose of propranolol was 212 ± 68 mg given in four divided doses daily.

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Beta-blocker therapy did not reduce the incidence of all-cause mortality (RR 0.24, 95% CI 0.01 to 4.75; participants = 70; low-quality evidence). Mortality attributed to Marfan syndrome was not reported. Non-fatal serious adverse events were also not reported. However, study authors report on pre-defined, non-fatal clinical endpoints, which include aortic dissection, aortic regurgitation, cardiovascular surgery and congestive heart failure. Their analysis showed no difference between the treatment and control groups in these outcomes (RR 0.79, 95% CI 0.37 to 1.69; participants = 70; low-quality evidence).

Beta-blocker therapy did not reduce the incidence of aortic dissection (RR 0.59, 95% CI 0.12 to 3.03), aortic regurgitation (RR 1.19, 95% CI 0.18 to 7.96), congestive heart failure (RR 1.19, 95% CI 0.18 to 7.96) or cardiovascular surgery, (RR 0.59, 95% CI 0.12 to 3.03); participants = 70; low-quality evidence.

The study reports a reduced rate of aortic dilatation measured by M-mode echocardiography in the treatment group (aortic ratio mean slope: 0.084 (control) vs 0.023 (treatment), P < 0.001). The change in systolic and diastolic blood pressure, total adverse events and withdrawal due to adverse events were not reported in the treatment or control group at study end point.

We judged this study to be at high risk of selection (allocation concealment) bias, performance bias, detection bias, attrition bias and selective reporting bias. The overall quality of evidence was low. We do not know whether a statistically significant reduced rate of aortic dilatation translates into clinical benefit in terms of aortic dissection or mortality.

Authors' conclusions

Based on only one, low-quality RCT comparing long-term propranolol to no treatment in people with Marfan syndrome, we could draw no definitive conclusions for clinical practice. High-quality, randomised trials are needed to evaluate the long-term efficacy of beta-blocker treatment in people with Marfan syndrome. Future trials should report on all clinically relevant end points and adverse events to evaluate benefit versus harm of therapy.

PLAIN LANGUAGE SUMMARY

Beta-blocker treatment in Marfan syndrome

Question
Do the benefits of beta-blocker therapy for Marfan syndrome outweigh the harms, as compared to placebo or no treatment?

Background
Marfan syndrome is a hereditary disorder affecting multiple systems in the body. Enlargement of the aorta (the largest blood vessel that carries blood out of the heart) is one of the most common and important features of this disease. It can lead to life-threatening problems, such as aortic dissection, which is a tear in the inner walls of the aorta causing blood to escape into the layers of the aortic wall, accumulate and potentially rupture.

Beta-blockers, a group of drugs used to decrease blood pressure, have been recommended by guidelines as the first line medical treatment of Marfan syndrome. The exact mechanism of action of beta-blockers in Marfan syndrome is not known.

Search Date
The evidence is current to June 2017.

Study characteristics
We included one study of 70 participants aged 12 to 50 years old with Marfan syndrome, who were assigned to either a beta-blocker called propranolol or no treatment for an average duration of 9.3 years in the control (no treatment) group and 10.7 years in the treatment group.

Study funding source
This study was supported by grants from the National Institute of Health, the US Food and Drug Administration, and the National Marfan Foundation.

Key results and conclusions
Propranolol compared to no treatment did not reduce mortality or morbidity, including aortic dissection, aortic regurgitation (leaking of the aortic valve causing reverse blood flow into the heart), heart failure (inability to pump enough blood around the body), and heart surgery. However, it reduced the rate of enlargement of the aortic diameter. Harms have not been fully reported in this study. We judged this trial to have high risk of bias and low-quality evidence. This study provides inadequate evidence to inform people with Marfan syndrome, their families and care-providers.

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SUMMARY OF FINDINGS

Summary of findings for the main comparison. Beta-blockers compared with placebo, no treatment or surveillance only for preventing aortic dissection in Marfan's syndrome

Beta-blockers compared with placebo, no treatment or surveillance only for preventing aortic dissection in Marfan syndrome

Patient or population: people with confirmed diagnosis of Marfan syndrome

Settings: outpatient

Intervention: beta-blockers

Comparison: placebo or no treatment or surveillance only

Outcomes Follow-up: mean 9.3 years in control group and 10.7 years in treatment group	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	No of participants (studies)	Quality of the evidence (GRADE)	Comments
	Risk with placebo, no treatment or surveillance only	Risk with beta blockers				
All-cause mortality	**53 per 1000**	**13 per 1000** (1 to 250)	**RR 0.24** (0.01 to 4.75)	70 (1 RCT)	⊕⊕⊖⊖ **Low**[1,2]	
Clinically important non-fatal end point as defined by Shores 1994 **(**aortic dissection, aortic regurgitation, congestive heart failure, or cardiovascular surgery)	**316 per 1000**	**249 per 1000** (117 to 534)	**RR 0.79** (0.37 to 1.69)	70 (1 RCT)	⊕⊕⊖⊖ **Low**[1,2]	
Acute aortic dissection	**105 per 1000**	**62 per 1000** (13 to 319)	**RR 0.59** (0.12 to 3.03)	70 (1 RCT)	⊕⊕⊖⊖ **Low**[1,2]	
Aortic regurgitation	**53 per 1000**	**63 per 1000** (9 to 419)	**RR 1.19** (0.18 to 7.96)	70 (1 RCT)	⊕⊕⊖⊖ **Low**[1,2]	
Congestive heart failure	**53 per 1000**	**63 per 1000** (9 to 419)	**RR 1.19** (0.18 to 7.96)	70 (1 RCT)	⊕⊕⊖⊖ **Low**[1,2]	
Cardiovascular surgery	**105 per 1000**	**62 per 1000**	**RR 0.59**	70 (1 RCT)	⊕⊕⊖⊖ **Low**[1,2]	

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		(13 to 319)	(0.12 to 3.03)		
Aortic root diameter > 6 cm	**26 per 1000**	**31 per 1000** (2 to 480)	**RR 1.19** (0.08 to 18.24)	70 (1 RCT)	⊕⊕⊖⊖ **Low[1,2]**

*__The risk in the intervention group__ (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CI: confidence interval; **RCT**: randomised controlled trial; **RR:** risk ratio

GRADE Working Group grades of evidence

High quality: we are very confident that the true effect lies close to that of the estimate of the effect.
Moderate quality: we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low quality: our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.
Very low quality: we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

[1]Downgraded one step for risk of bias (high risk of selection, performance, detection, attrition and selective outcome reporting bias).
[2]Downgraded one step for very serious imprecision (wide confidence interval with very low event rate).

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BACKGROUND

Description of the condition

Marfan syndrome is a hereditary disorder affecting the connective tissue and is caused by a mutation of the fibrillin-1 (FBN1) gene. It was first discovered in 1896 by Professor Antoine-Bernard Marfan, a French paediatrician (Franken 2012; Judge 2005; Koracevic 2012). The condition is estimated to have an incidence of 1 in 2000 to 1 in 5000 individuals (Danyi 2012; Franken 2012; Von Kodolitsch 2007; Wright 2012).

Marfan syndrome affects multiple systems of the body, most notably the cardiovascular, ocular, skeletal, dural and pulmonary systems (Castellano 2012; Pyeritz 2009). Aortic root dilatation is the most frequent cardiovascular manifestation (Von Kodolitsch 2004), and its complications, including aortic regurgitation, dissection and rupture are the main cause of morbidity and mortality in people with this disease (Canadas 2010; Franken 2012). One long-term survival study of Marfan syndrome in the early 1970s showed the mean age of death to be 32 years for people who did not receive aortic surgery (Murdoch 1972).

Although other cardiovascular features such as valvular disease, endocarditis, cardiomyopathy and arrhythmias exist in these people with Marfan syndrome (Pyeritz 2000; Von Kodolitsch 2004), dissection of the aorta has been, and remains, the most common cause of death (Pyeritz 2008; Silverman 1995). Aortic wall weakness, aortic dilatation and arterial hypertension are the major mechanisms of dissection and rupture (Von Kodolitsch 2004). Research has shown that a defect in the FBN1 glycoprotein, a major constituent of the extracellular matrix microfibrils (Bunton 2001), leads to poor structural and functional integrity of the normal vessel wall by several potential mechanisms (Danyi 2011; Judge 2005; Von Kodolitsch 2007). The changes in the walls of the elastic arteries occur primarily in the medial layer and are associated with less distensibility and increased stiffness leading to consequent weakening and dilatation, beginning in the sinuses of the aortic root and extending to the proximal ascending aorta (Pyeritz 2000; Pyeritz 2009).

Aortic root pathology has hence become the most important target for improving survival in people with Marfan syndrome (Vaidyanathan 2008). As a result of improved diagnosis, careful monitoring, lifestyle guidance, medical and especially surgical management of this disease, the life expectancy of people with Marfan syndrome has increased by at least 30 years (Pyeritz 2009; Silverman 1995). Although the benefits of prophylactic aortic surgery have been clearly demonstrated, the value of reducing aortic dilatation medically is unclear in the clinical setting to reduce morbidity and mortality.

Description of the intervention

The primary aim of pharmacological therapy for Marfan syndrome is to slow down the rate of aortic dilatation with the goal to delay or prevent complications and surgical interventions (Franken 2012). The beta-blockade strategy began in 1971 when Halpern and colleagues suggested that the reduction of the rate of increase in aortic pressure over time was an important additional factor to lowering blood pressure alone in decreasing haemodynamic stress on the proximal aorta (Halpern 1971; Keane 2008; McKusick 2004). Beta-blockers became, and have remained, the standard preventive treatment since the mid-1990s when one randomised controlled trial (RCT), Shores 1994, concluded that prophylactic beta-adrenergic blockade with propranolol slowed the rate of aortic dilatation and reduced the development of aortic complications in people with Marfan syndrome. Subsequent studies have shown varying results on the efficacy of beta-blockade therapy (Legget 1996; Rios 1999; Tierney 2007). Despite the lack of conclusive evidence, it has been recommended that people with Marfan syndrome and aortic aneurysm should be prescribed beta-blockers to reduce the rate of dilatation unless contraindicated (Boodhwani 2014; Hiratzka 2010; Pyeritz 2012; Wright 2012). Current beta-blockers in use include propranolol, atenolol and metoprolol (Wright 2012). Atenolol is currently the drug of choice as it has a longer half-life and is more cardioselective than propranolol, with fewer side effects (Keane 2008). The drug dosage is adjusted according to heart rate, aiming to maintain a rate of 60 to 70 beats per minute at rest and fewer than 100 beats per minute after sub-maximal exercise (Canadas 2010; Loeys 2010; Wright 2012). Beta-blockers have a significant side-effect profile and documented adverse effects include bronchospasm, exercise intolerance, fatigue, depression, and first- and third-degree heart block (Gao 2011; Shores 1994).

Other anti-hypertensive medications such as calcium channel blockers, angiotensin-converting enzyme (ACE) inhibitors and, more recently, angiotensin receptor blockers (ARB) have been studied with mixed results (Bhatt 2015; Lacro 2014; Milleron 2015; Rossi-Foulkes 1999; Topouchian 1998; Williams 2012; Yetman 2005). Several large RCTs assessing the effect of losartan (an angiotensin II type I receptor blocker) have recently been completed or are underway (Forteza 2016; Gambarin 2009; Lacro 2014; Mullen 2013; Moberg 2012). The use of an ACE inhibitor or an ARB is suggested for people who are unable to tolerate beta-blockers or as an add-on therapy if beta-blockade monotherapy is unsuccessful at controlling blood pressure (Keane 2008; Pyeritz 2014; Singh 2016; Wright 2012). The Marfan Treatment Trialists' Collaboration has proposed a large, prospective, collaborative meta-analysis of all the RCTs evaluating ARB treatment in Marfan syndrome (Pitcher 2015).

How the intervention might work

Although the exact mechanism of beta-blockers in Marfan syndrome is unknown, the potential benefits have been attributed to their negative inotropic and chronotropic effects, resulting in a reduction in aortic wall stress (Canadas 2010). This is important in decreasing the progression of aortic dilatation as the degree of increase in aortic root diameter is a major indicator for the risk of dissection (Judge 2005). The anti-arrhythmic and anti-fibrillatory effects of beta-blockade are also believed to be advantageous as other cardiovascular manifestations such as mitral valve prolapse and left ventricular dilatation are common in Marfan syndrome, pre-disposing people to arrhythmias (Koracevic 2012).

The cardiac cycle is pulsatile in nature, with aortic expansion during systole and recoil during diastole. This pulsatile flow can be characterised by a change in pressure over time and contributes to the progression of aortic dissection compared with non-pulsatile flow (Castellano 2012; Liao 2010). The aorta buffers the level of fluctuation between the extreme pressures of systole and diastole, allowing a nearly continuous blood flow from the central to the peripheral vascular system (Belz 1995; Koracevic 2012). This protective function, known as the Windkessel effect, relies on the elasticity of the aorta (Belz 1995), and, as Marfan syndrome is

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associated with abnormal aortic elastic properties (Hirata 1991), people are therefore compromised. Studies have shown that beta-blocker therapy may directly affect the aortic wall by increasing its distensibility, and decreasing aortic stiffness and pulse-wave velocity (Groenink 1998; Ladouceur 2007; Rios 1999). With the favourable effects of beta-blockers on change in pressure over time, this pharmacological intervention became important in the medical management in aortic dissection (Castellano 2012; Danyi 2012; Liao 2010).

Why it is important to do this review

Beta-blockers have remained the standard treatment for the prevention of aortic complications since medical intervention was introduced in the 1970s. Studies investigating the efficacy and therapeutic benefit of beta-blockade have produced heterogeneous and conflicting results, leading to much debate on their life-long use for people with Marfan syndrome (Ladouceur 2007; Tierney 2007). One meta-analysis, Gersony 2007, included six studies, of which only one was an RCT, and concluded that there was no evidence that beta-blocker therapy had clinical benefit in people with Marfan syndrome. Conversely, Gao 2011 concluded from their meta-analysis that routine prescription of beta-blockers may offer substantial benefit on clinical end points for children and adolescents with Marfan syndrome.

One Cochrane Review on the medical treatment for small abdominal aortic aneurysms (AAA) reported that there was no significant difference in AAA expansion or cardiovascular end points between beta-blocker treatment and placebo. Furthermore, a significantly increased number of people discontinued beta-blocker therapy for AAA management due to adverse effects and there was no significant difference in the combined overall mortality of the three included propranolol trials (Rughani 2012). Although thoracic aortic aneurysms (TAA) are more common in Marfan syndrome and extrapolating data from AAA to TAA studies should be conducted with caution (Castellano 2012), these findings do raise cause for concern.

Lifelong treatment, as beta-blockade therapy in Marfan syndrome currently remains, is not a decision or commitment that should be taken lightly. Even with the anticipation of other pharmacological treatments currently under trial, it is important to establish the efficacy of the baseline treatment that has been in place for decades. This would hopefully decrease the discrepancy gap between clinical practice and current evidence, and provide the physician with more options to optimise and individualise a management plan for his/her patient. Since aortic pathology is present in the vast majority of people with Marfan syndrome, and is the most life-threatening manifestation of this disease (Canadas 2010; Franken 2012; Gao 2011; Judge 2005), this review will focus on the effects of beta-blockers for preventing aortic dissection in Marfan syndrome. Therefore, we will examine the most up-to-date literature to assess the long-term efficacy of this treatment in people of all ages with Marfan syndrome and determine if current practice with life-long beta-blocker therapy is evidence-based.

OBJECTIVES

To assess the long-term efficacy and safety of beta-blocker therapy as compared to placebo, no treatment or surveillance only in people with Marfan syndrome.

METHODS

Criteria for considering studies for this review

Types of studies

All randomised controlled trials (RCTs) of at least one year in duration assessing the effects of beta-blocker monotherapy in people with Marfan syndrome were eligible for inclusion.

Types of participants

We included participants of all ages with a confirmed diagnosis of Marfan syndrome and excluded people with previous aortic root surgery, planned aortic surgery within one year of study enrolment, previous aortic dissection and co-existing diagnoses of connective tissue disease. We also excluded pregnancy in people with Marfan syndrome.

Types of interventions

We assessed beta-blocker monotherapy compared with placebo, no treatment or surveillance only.

Types of outcome measures

Primary outcomes

1. All-cause mortality (including mortality attributed to Marfan syndrome)
2. All non-fatal serious adverse events (including all-cause hospitalisations, cardiovascular events such as aortic dissection or rupture, and cardiovascular surgery)

Secondary outcomes

1. Measurements of the aortic root diameter taken by echocardiogram or other imaging modalities
2. Systolic and diastolic blood pressure
3. Total adverse events
4. Withdrawals due to adverse events

Search methods for identification of studies

Electronic searches

We identified trials through systematic searches of the following bibliographic databases on 28 June 2017:

1. Cochrane Central Register of Controlled Trials (CENTRAL; 2017, Issue 5) in the Cochrane Library
2. Epub Ahead of Print, In-Process & Other Non-Indexed Citations, MEDLINE Daily and MEDLINE (Ovid, 1946 to 28 June 2017)
3. Embase (Ovid, 1980 to Week 26, 2017)
4. Science Citation Index Expanded and the Conference Proceeding Citation Index - Science, Web of Science Core Collection (Thomson Reuters, 1970 to 28 June 2017)

We adapted the search strategy for MEDLINE (Ovid) (Appendix 1) for use in the other databases. The Cochrane sensitivity-maximising RCT filter was applied to MEDLINE (Ovid) (Lefebvre 2011) and an adaptation of it to Web of Science. For Embase, we applied RCT filter terms as recommended in the *Cochrane Handbook for Systematic Reviews of Intrventions* (Lefebvre 2011). Additionally, we applied an adverse events filter to MEDLINE and Embase (Loke 2011).

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We also searched the Online Metabolic and Molecular Bases of Inherited Disease (OMMBID) and sought to identify ongoing, recently completed or unpublished trials by searching clinical trials registers; ClinicalTrials.gov (www.ClinicalTrials.gov) and the World Health Organization (WHO) International Clinical Trials Registry Platform (ICTRP) Search Portal (apps.who.int/trialsearch/), using the terms 'Marfan syndrome' or 'Marfan syndrome' (last updated search on 30 June 2017).

We did not impose any restriction on language of publication.

Searching other resources

We examined reference lists of eligible studies and reviewed articles manually for additional references. We contacted the authors of the included study for missing data via email.

Data collection and analysis

Selection of studies

Two review authors (HK and KL) independently reviewed the titles and abstracts of all potential studies identified by the search strategy outlined above. We initially screened studies and coded them as 'Yes', 'Maybe' or 'No'. We resolved discrepancies by consensus or discussion with the third review author (VM).

For inclusion, a trial had to meet the following criteria:

1. the study was a RCT;
2. the study population had a diagnosis of Marfan syndrome;
3. the intervention was beta-blocker mono-therapy compared with placebo, no treatment, or surveillance only;
4. the study reported one or more primary or secondary outcome measures.

We obtained full-text versions of all potentially eligible studies and made a decision for inclusion or exclusion. Where there were any differences in opinion regarding the suitability of a study, we discussed these with the third review author (VM). We included detailed trial reports where methodology could be assessed.

Data extraction and management

Two review authors (HK and VM) independently extracted relevant data from the retrieved articles using a data extraction form (Appendix 2). We resolved any disagreement in the data extraction and management by discussion.

Assessment of risk of bias in included studies

Two review authors (HK and KL) independently assessed the risk of bias for the included study. We performed this assessment of methodological quality according to the criteria described in Chapter 8 of the *Cochrane Handbook for Systematic Reviews of interventions* (Higgins 2011), and included the following:

1. random sequence generation;
2. allocation concealment;
3. blinding of participants and personnel;
4. blinding of outcome assessment;
5. incomplete outcome data;
6. selective outcome reporting;
7. other bias.

Each domain was allocated as either 'low, high or unclear risk'. We resolved any disagreements by discussion with the third author (VM).

Measures of treatment effect

We summarised dichotomous data (all-cause mortality, non-fatal serious adverse events, total adverse events and withdrawal due to adverse events) using risk ratios (RR) with 95% confidence intervals (CI) where relevant and when data were available. We planned to use mean differences (MD) with 95% CI to summarise continuous outcomes (measurement of aortic diameter, systolic and diastolic blood pressure).

Unit of analysis issues

For dichotomous outcomes, the unit of analysis was the number of individuals assigned to beta-blocker treatment and the number of individuals assigned to the control group. For continuous outcomes, we planned the unit of analysis was to be the mean, standard deviation, and the number of individuals in the treatment and control groups (Deeks 2011).

Dealing with missing data

One trial, Shores 1994 met the inclusion criteria. We used data available in the publication and also contacted the study authors via email for additional information regarding missing data. The study protocol was not available. This study is not registered with ClinicalTrials.gov.

Assessment of heterogeneity

As only one trial met the inclusion criteria, we could not perform heterogeneity assessments. If sufficient numbers of studies had been available, we would have performed a Chi^2 test to determine the presence of statistical heterogeneity at a significance level of P value less than 0.10. If more studies become available in the future, we will assess the quantity of heterogeneity using the I^2 statistic (Higgins 2003) with the following parameters:

1. I^2 = 0% to 40% heterogeneity may not be important;
2. I^2 = 30% to 60% may represent moderate heterogeneity;
3. I^2 = 50% to 90% may represent substantial heterogeneity;
4. I^2 = 75% to 90% considerable heterogeneity.

Assessment of reporting biases

If we identified at least 10 studies, we planned to assess reporting bias by reviewing the funnel plots and performing a linear regression test. As only a single study met the inclusion criteria we could not assess reporting bias.

Data synthesis

We used the most recent version of the Cochrane Review Manager 5 software (RevMan 5) for data synthesis and analysis (RevMan 2014). We utilised a fixed-effect model and all data are accompanied by the 95% CI.

Subgroup analysis and investigation of heterogeneity

As only one study met the inclusion criteria, we did not perform subgroup analysis. If sufficient numbers of trials were available, we had planned to perform the following subgroup analyses:

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1. severity of disease at baseline: mild, moderate or severe;
2. sex: female versus male;
3. age groups: children/adolescents versus adults.

Sensitivity analysis

We did not perform sensitivity analysis as only one trial met the inclusion criteria. If sufficient numbers of trials were available, we had planned to assess the following features of methodological quality of included studies: sequence generation, allocation concealment, blinding of participants and assessors, and incomplete outcome data.

RESULTS

Description of studies

Results of the search

We screened a total of 1819 references from databases, trials registers and handsearching after de-duplication. We retrieved 15 full-text articles for further assessment. Only one study fulfilled the eligibility criteria for inclusion (Shores 1994). See study flow diagram (Moher 2009) (Figure 1).

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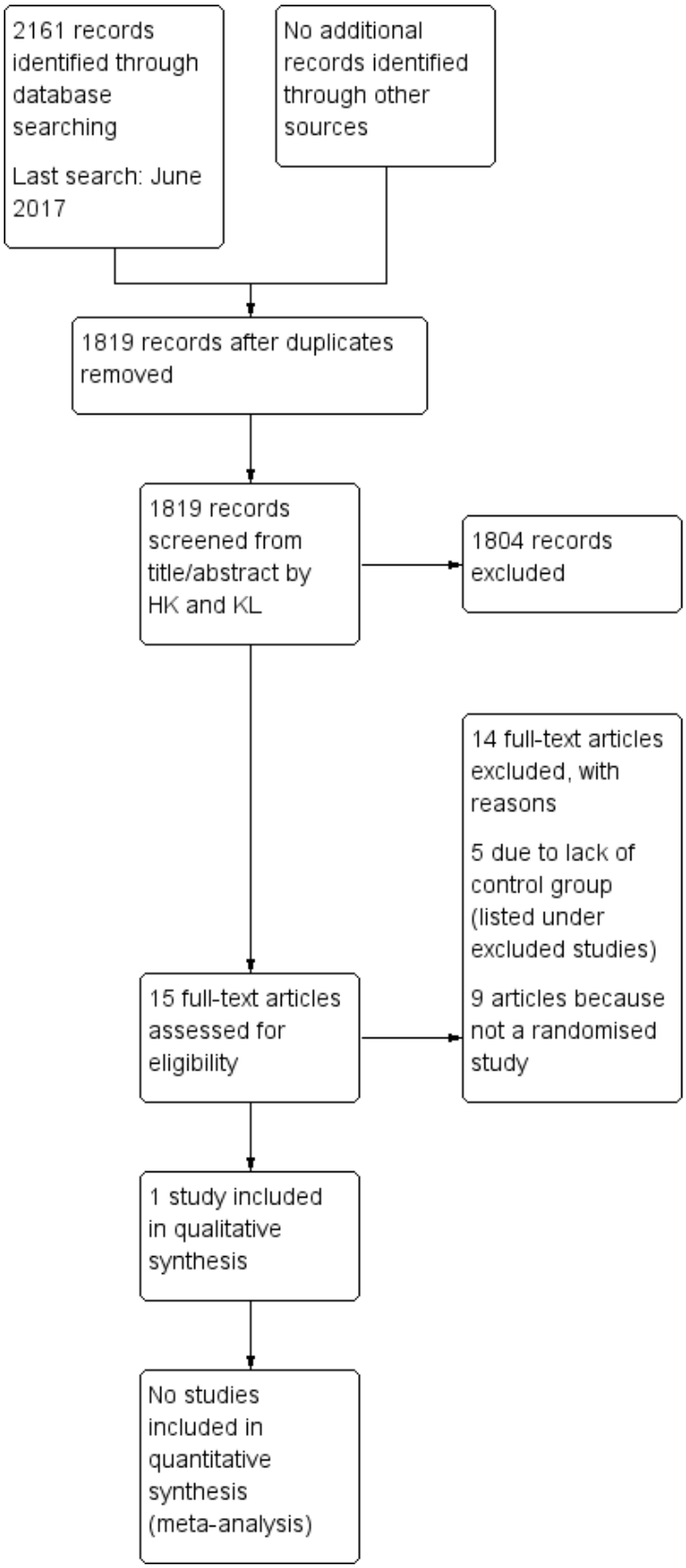
Figure 1. Study flow diagram



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Included studies

The one included study by Shores 1994, titled 'Progression of aortic dilatation and the benefit of long-term β-adrenergic blockade in Marfan syndrome' is an open-label, randomised trial that included adolescent and adult participants with Marfan syndrome to receive either beta-blocker (propranolol) or no treatment.

This single-centre study recruited participants who met the international diagnostic criteria for Marfan syndrome (Beighton 1988) within one year of trial initiation. Participants less than 12 or more than 50 years old, or receiving ongoing treatment with propranolol were excluded. Other exclusion criteria included: aortic dissection, aortic regurgitation on auscultation, moderate or severe mitral regurgitation, previous cardiovascular surgery, dyspnea during moderate exercise, orthopnoea, peripheral oedema, left ventricular ejection fraction less than 50%, atrioventricular conduction delay of any degree, and disorders where propranolol was contraindicated.

Of 117 people considered for the study, 93 were eligible and 70 provided informed consent. Participants were randomised after giving consent by assigning the next available number on a list derived from a table of random numbers. 38 participants with even numbers received no treatment (control group) and 32 participants with odd numbers received propranolol (treatment group). Participants who were eligible for the study but who chose not to participate did not differ appreciably in any of the characteristics from participants in the control and treatment groups combined.

The two study groups were matched for sex (male:female, control 19:18, treatment 20:12), mean age (control vs treatment; 14.5 years vs 15.4 years), and proportion of participants less than 18 years old. Baseline cardiovascular characteristics including aortic root diameter, presence of mitral-valve prolapse or regurgitation, blood pressure, heart rate and systolic time interval were recorded. In the treatment group, male participants had a significantly lower resting heart rate compared to the female participants. Additionally, the treatment group had a significantly greater aortic diameter at baseline compared to the control group, but did not differ significantly in aortic ratio.

Neither participant nor investigator was blinded to the study. The initial dose of propranolol was 10 mg four times daily in the treatment group. This was adjusted according to individual response of heart rate to exercise and systolic interval, assessed after two to four weeks of initiation. Optimal dose was reached when the heart rate remained below 100 beats per minute during exercise or the systolic time interval increased by 30%. The mean (± standard error (SE)) dose of propranolol was 212 ± 68 mg given in four divided doses daily. The time-point at which this optimal dose was achieved is not provided.

Participants were reviewed every 6 to 12 months with history and physical examination, electrocardiography and echocardiography. Serum drug concentration and phonocardiography to measure the left ventricular systolic time interval were also evaluated in the treatment group to assess for optimal dosing.

Participants remained in the study until one of the following endpoints was reached: voluntary withdrawal, death, aortic dissection, aortic regurgitation detected by auscultation, cardiovascular surgery, congestive heart failure or an intractable adverse reaction to propranolol. The published study states that all comparisons of the two study groups included all participants, according to the intention-to-treat (ITT) principle. However, the study authors, through personal communication, confirmed that no clinically relevant endpoints were collected during the follow-up period of 9.3 years in the control group and 10.7 years in the treatment group, therefore they did not perform an ITT analysis at the end of follow-up.

Further details of the included study are presented in Characteristics of included studies.

Excluded studies

We obtained the full-text versions for fifteen studies in total. Reasons for exclusion of five studies are presented in Characteristics of excluded studies. The other nine studies were not RCTs and did not meet the inclusion criteria.

Risk of bias in included studies

We have summarised the risk of bias of the included study (Shores 1994) in Figure 2 and also provided a detailed explanation in the 'Risk of bias' table. Based on the information available in the published study and through personal communication with the study authors, we considered the trial to have a low risk of random sequence generation (selection) bias and a high risk of allocation concealment (selection) bias. There was high risk of performance bias, detection bias, attrition bias and reporting bias, and an unclear risk of other bias.

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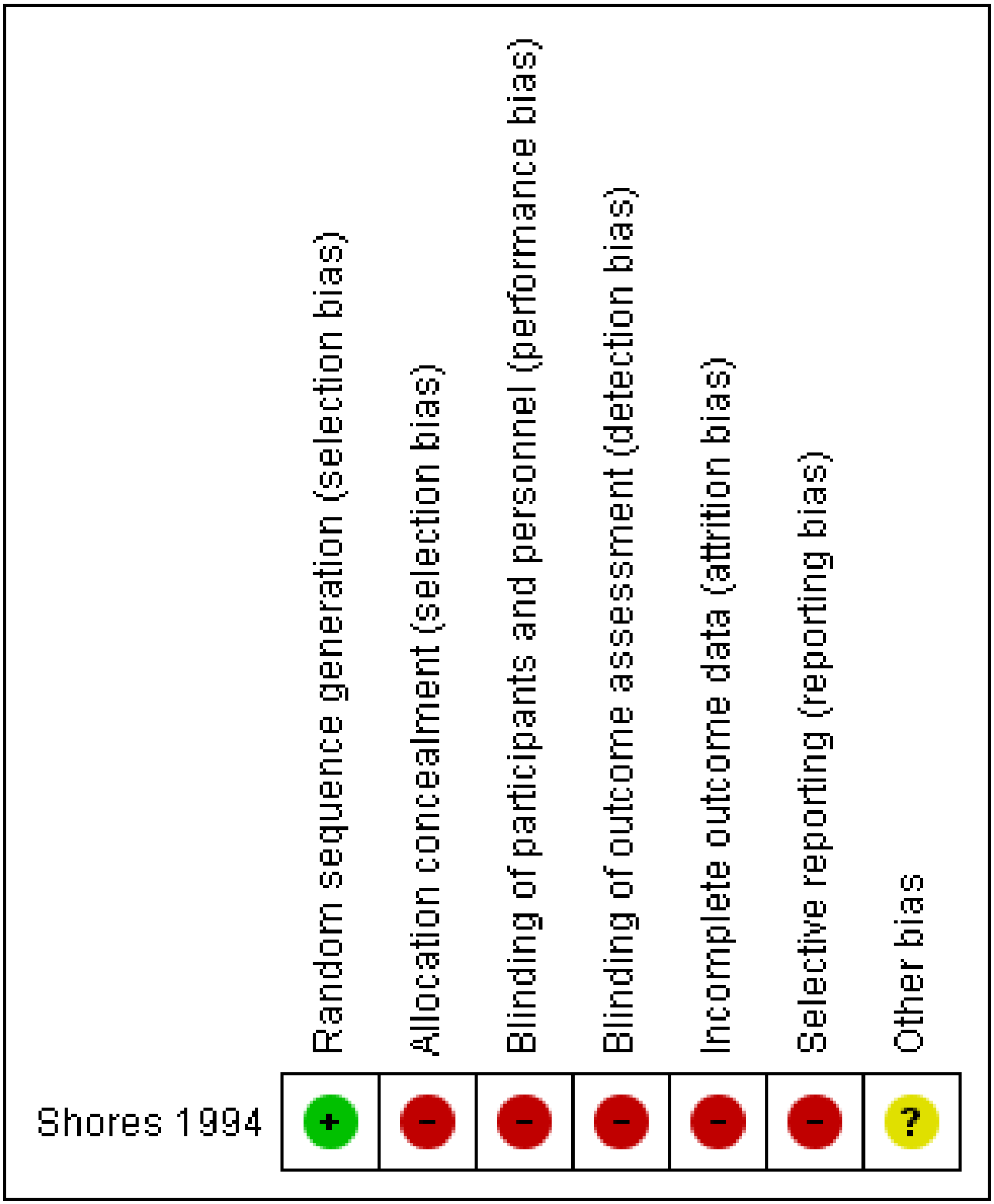
Figure 2. Risk of bias summary: review authors' judgements about each risk of bias item for each included study



Allocation

After obtaining consent, participants were randomised by assigning the next available number from a list derived from a table of random numbers at the beginning of the study. Participants with an even number received no treatment (control group), and participants with an odd number received propranolol (treatment group). We therefore judged the study at low risk of bias for random sequence generation, however, the study author, through personal communication, stated that investigators were aware of treatment

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allocation and therefore we judged the study at high risk of bias for allocation concealment.

Blinding

This was an open-label study with both participants and investigators aware of treatment allocation and therefore at high risk of performance bias. Echocardiographic data were interpreted throughout the study by the same investigator who was unaware of the participant's identity, age, study group, or the sequence of multiple tracings, and therefore considered low risk of bias. However, for all other outcomes, we judged a high risk of detection bias as outcome assessors were not blinded.

Incomplete outcome data

Withdrawal due to clinical end-points was described, but the total withdrawals from the study was not. Furthermore, once participants reached a clinical end-point, they were withdrawn and further follow-up was not documented (confirmed by the study author). The published study states that all comparisons included all participants according to the ITT principle. However, the study author, through personal communication, confirmed that no clinically relevant endpoints were collected during the follow-up period of 9.3 years in the control group and 10.7 years in the treatment group, therefore they did not perform an ITT analysis at the end of follow-up. We therefore judged the study at high risk of attrition bias. The study author stated that there were no missing data and the last observation was carried forward.

Selective reporting

We judged the study at high risk of reporting bias. The study protocol was not available and this was confirmed by the author through personal communication. Not all endpoints described in the methods are reported in the published study including: voluntary withdrawal, cardiovascular surgery, congestive heart failure indicated by new-onset dyspnoea, orthopnoea, peripheral oedema, or fatigability associated with a left ventricular ejection fraction of less than 40%, and intractable adverse reaction to propranolol. Data regarding two of these outcomes: cardiovascular surgery and congestive heart failure, were provided by the study author through personal communication. Additionally, in the published study, it appears that "aortic root > 6 cm" was added as a clinical end-point in addition to those stated in the methods section, however the study author states that this was a pre-determined clinical end-point. Furthermore, adverse effects data were not collected systematically between groups as the study was not blinded or placebo-controlled. The study stated that a propranolol dose reduction from 80 mg to 40 mg was required for one participant who developed third-degree atrioventricular block. Personal communication with the study author reports that no adverse events occurred in the control group.

Other potential sources of bias

This study was supported by grants from the National Institute of Health, the Food and Drug Administration and the National Marfan Foundation. However other bias is unclear as findings from this study have not been replicated as only a single study met the inclusion criteria. The study author, through personal communication, confirmed that no power calculation was performed to determine the sample size.

Effects of interventions

See: **Summary of findings for the main comparison** Beta-blockers compared with placebo, no treatment or surveillance only for preventing aortic dissection in Marfan's syndrome

Primary outcomes

1. All-cause mortality (including mortality attributed to Marfan syndrome)

Two deaths (2.8%) were observed in the study, both in the control group. The two participants, a 14 year-old boy and an 18 year-old woman, had mitral-valve prolapse and a history of paroxysmal tachyarrhythmia (one of whom had Wolff-Parkinson-White syndrome). No aortic dissection or obvious cause of death was identified in postmortem examinations for either participant. The time points at which these participants died were not provided. No mortality attributed to Marfan syndrome was reported. There was no difference between the two study groups in all-cause mortality (RR 0.24, 95% CI 0.01 to 4.75; participants = 70; studies = 1; low-quality evidence). See Analysis 1.1.

2. All non-fatal serious adverse events (including all-cause hospitalisations, cardiovascular events such as aortic dissection or rupture, and cardiovascular surgery)

All non-fatal serious adverse events as defined above were not reported in the included study.

Important non-fatal clinical end points

Other morbidity outcomes as defined and reported by the Shores 1994 study included aortic dissection, aortic regurgitation, congestive heart failure and cardiovascular surgery.

Information regarding congestive heart failure and cardiovascular surgery were provided by the study author through personal communication. Cardiovascular surgery was indicated in participants when aortic root diameter reached 6 cm.

Twelve participants in the control group and eight participants in the treatment group reached these non-fatal clinical endpoints. However, two participants in the treatment group had never taken their propranolol. Analysis showed no difference between the two study groups (RR 0.79, 95% CI 0.37 to 1.69; participants = 70; studies = 1; low-quality evidence). See Analysis 1.2.

Acute aortic dissection was reported in four participants in the control group and two participants in the treatment group. Analysis showed no difference between the two study groups (RR 0.59, 95% CI 0.12 to 3.03; participants = 70; studies = 1; low-quality evidence). See Analysis 1.3.

Aortic regurgitation was reported in two participants in the control group and two participants in the treatment group. Analysis showed no difference between the two study groups (RR 1.19, 95% CI 0.18 to 7.96; participants = 70; studies = 1; low-quality evidence) See Analysis 1.4.

Congestive heart failure was reported in two participants in the control group and two participants in the treatment group. Analysis showed no difference between the two study groups (RR 1.19, 95% CI 0.18 to 7.96; participants = 70; studies = 1; low-quality evidence) See Analysis 1.5.

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Cardiovascular surgery was reported in four participants in the control group and two participants in the treatment group. Analysis showed no difference between the two study groups (RR 0.59, 95% CI 0.12 to 3.03; participants = 70; studies = 1; low-quality evidence) See Analysis 1.6.

Secondary outcomes

1. Measurements of the aortic root diameter taken by echocardiogram or other imaging modalities

Echocardiography was used to measure aortic diameter. M-mode echocardiography was utilised until 1982 when cross-sectional examinations were performed. The study states that for conformity, only M-mode tracings by the leading-edge method were analysed to determine aortic diameter. Maximal diameter, usually at the level of the sinuses, but occasionally at the sino-tubular junction was measured in five consecutive cycles and averaged. We note that there is discrepancy between the manuscript text where it states that mean values were presented with standard errors, and the table of patient characteristics, where the values are stated as means with standard deviations.

The two study groups differed significantly in their initial aortic diameter (control vs treatment: 30.2 mm vs 34.6 mm). Initial mean aortic ratio did not differ significantly (1.3 vs 1.4) and therefore we treated it as a co-variable in the analysis. The aortic ratio was calculated by dividing the measured aortic diameter by the diameter predicted from the participant's height, weight and age. Of the two participants reaching the clinical endpoint of aortic root greater than 6 cm, the initial aortic ratio of one participant in the control group was 1.4 vs 2.1 in the other participant in the treatment group. Table 1 provides information on the initial aortic diameter and ratio reported at baseline.

The study reports that the rate of aortic ratio increase was significantly lower in the treatment group compared to the control group (mean slope of the aortic ratio plotted against time for treatment vs control: 0.023 vs 0.083 per year), ($t = 6.73$, $P < 0.001$; $z = 6.64$ by Mann Whitney nonparametric rank-sum test, $P < 0.001$). The study authors also report little, if any relation between the rate of change in aortic ratio and the initial aortic diameter. Additionally, analysis of covariance showed that adjustment for the initial aortic diameter had a negligible effect on the significance of the difference in the rates of enlargement. We were unable to measure the treatment effect on aortic ratio as these data were unavailable.

The study states that participants from both study groups who reached an endpoint had higher average initial aortic ratios than the total study population. Again, data were unavailable to perform statistical analysis.

The study does report on participants with aortic root diameter greater than 6 cm. One participant in the control group and one participant in the treatment group reached this end point. Although not stated in the published study, the study author, through personal communication, confirmed that this was a pre-determined clinical end point. Analysis showed no difference between the two study groups (RR 1.19, 95% CI 0.08 to 18.24; participants = 70; studies = 1; low-quality evidence) See Analysis 1.7.

2. Systolic and diastolic blood pressure

Table 2 provides information on the blood pressure measured at baseline and during optimal dose.

Systolic and diastolic blood pressure values were reported at baseline but not at study endpoint therefore we could not perform analysis of magnitude of blood pressure reduction between beta-blocker and no-treatment groups.

Blood pressure data in the treatment group were reported when the optimal doses of propranolol were achieved.

1. In the male treatment group, the study reported a significant decrease in blood pressure values during optimal treatment dose as compared to baseline (systolic: $P = 0.006$, diastolic: $P = 0.045$).
2. In the female treatment group, the study reported a decrease in blood pressure values during optimal treatment dose as compared to baseline (systolic: $P = 0.06$, diastolic: $P = 0.051$) however, the P values were not significant.

3. Total adverse events

As the study was not blinded or placebo-controlled, the control group was not queried systematically about adverse symptoms. The investigators reported that there was no atrioventricular conduction delay in the control group. The study author, through personal email communication, provided additional information regarding adverse events in the control group (see Table 3, which provides information on adverse effects of long-term treatment for 30 participants complying with beta-blocker therapy).

4. Withdrawals due to adverse events

Shores 1994 does not discuss any loss to follow-up or withdrawals due to adverse events. The study author, through personal communication, confirmed that information on adverse events after participants withdrew from the study was not collected or documented.

DISCUSSION

Summary of main results

The single study included in this review (Shores 1994) is an open-label, randomised, single-centre trial comparing beta-blocker monotherapy with no treatment in 70 participants aged 12 to 50 years old with Marfan syndrome. Participants were randomly assigned to propranolol (N = 32) or control (N = 38) for an average duration of 9.3 years in the control group and 10.7 years in the treatment group.

Propranolol was initiated at 10 mg four times daily, then individually up-titrated to an optimal dose when the heart rate remained below 100 beats per minute during exercise or the systolic time interval increased by 30%. The mean (± SE) optimal dose of propranolol was 212 ± 68 mg given in four divided doses daily.

There was no significant difference between the two study groups in all-cause mortality. No mortality attributed to Marfan syndrome was reported. All non-fatal serious adverse events were not reported. However, the study authors reported pre-defined non-fatal clinical endpoints that included aortic dissection, aortic regurgitation, congestive heart failure, and cardiovascular surgery. Their analysis showed no difference between the treatment and

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control groups in these outcomes. Additionally, beta-blocker therapy did not reduce the incidence of acute aortic dissection, aortic regurgitation, congestive heart failure or cardiovascular surgery.

The trial authors reported a significantly reduced rate of aortic dilatation measured by M-mode echocardiography in the treatment group (aortic ratio mean slope: 0.084 (control) vs 0.023 (treatment), P < 0.001). All other secondary outcomes (systolic and diastolic blood pressure, total adverse events and withdrawal due to adverse events) were not adequately reported in the treatment or control group at the study end-point and therefore could not be analysed.

We judged this trial to be at low risk of random sequence generation but high risk of selection (allocation concealment) bias, performance bias, detection bias, attrition bias and selective reporting bias.

Overall completeness and applicability of evidence

Overall completeness

Only one RCT satisfied the inclusion criteria for this review. The sample size calculation was not reported. The power of the study to detect a difference in the aortic root dimensions (the primary outcome measure) was not reported.

Primary outcomes

Although all-cause mortality from both study groups was reported, it was not the trial's primary outcome and considered as one of numerous clinical end-points. It is therefore difficult to interpret all-cause mortality, as participants withdrawn for other reasons were not followed up to the study's completion. We commend the average study duration (9.3 and 10.7 years in the control and treatment groups respectively), however, the rationale for this length is unclear as no protocol was available. Each participant differed in the length of follow-up according to whether pre-defined end-points were reached, but individual participant data for this were not provided. The study authors report on the clinical end-points reached, however no data were presented on other reasons for withdrawal.

Other primary outcomes pre-defined by the review were not fully reported in the published article as previously described. Personal communication with the study authors by email resulted in obtaining important information regarding other non-fatal clinical outcomes such as congestive heart failure and participants undergoing cardiovascular surgery.

Secondary outcomes

Aortic root dimensions, considered the primary outcome by Shores 1994, were measured by M-mode echocardiography throughout the study duration to maintain conformity. This single modality is however a key limitation, as the current gold standards employ cardiovascular computed tomography (CT) or magnetic resonance imaging (MRI) to confirm the echocardiographic measurements of the aortic diameter (Hiratzka 2010, Wright 2012). Although all echocardiographic data were interpreted by the same investigator, ruling out inter-observer variability in the study, this measurement tool is still prone to intra-observer variability and error.

It is also important to note that the initial aortic diameter was significantly different between the study groups and the Shores 1994 investigators accounted for this by measuring aortic ratio as a parameter and assessing the rate of change in aortic ratio as a function of the initial aortic diameter. However, they did not provide timelines for the two participants (one from each study group) who reached the clinical end-point of aortic root greater than 6 cm despite the differing initial aortic ratios (1.4 in control, 2.1 in treatment).

The rationale for the study was the effect of beta-blockade on arterial haemodynamic function. Although the study provided blood pressure, heart rate and systolic time-interval measurements at baseline for both study groups, these parameters were not provided for the study end-point and only reported for the treatment group when optimal dose was achieved. Correlation with haemodynamic function with aortic root dimensions would have provided valuable information.

Other limitations of the study are the open-label design and lack of placebo in the control group. The adverse effects of long-term beta-blocker therapy were not reported in the published study for either group, however personal communication with the study authors confirmed that there were no adverse effects in the control group. The timeline to when the adverse effects reported for the treatment group have not been provided. Although the study states that serum propranolol levels were taken, these data were not available in the published manuscript.

Applicability of evidence

The authors of this review feel that the applicability of the evidence is limited and can be broadly summarised in two categories:

Intervention

Current guidelines recommend beta-1 selective agents such as atenolol or metoprolol and it is therefore difficult to determine the appropriate dosing schedules for these drugs as this trial used propranolol. It is recommended that dosing is adjusted to maintain a heart rate after submaximal exercise to less than 100 beats per minute in adults and less than 110 beats per minute in children (Wright 2012).

When this study began, propranolol, a non-selective beta-adrenergic blocker was the only preparation available for clinical use. Propranolol was the only beta-blocker studied as compared to control. We did not identify any RCTs comparing atenolol or metoprolol to control in people with Marfan syndrome.

Population

This evidence cannot be applied to people with Marfan syndrome with aortic dissection, aortic regurgitation, moderate or severe mitral regurgitation, previous cardiovascular surgery, those with dyspnoea due to moderate exercise, orthopnoea or peripheral oedema, left ventricular ejection fraction of less than 50%, atrioventricular conduction delay of any degree, and those with disorders in which propranolol is contraindicated (diabetes mellitus or recurrent bronchospasm requiring medical treatment).

Further, the current best recognised tool to diagnose Marfan syndrome is the Revised 2010 Ghent nosology criteria (Loeys 2010), first proposed in 1996 (De Paepe 1996) to overcome the tendency to over-diagnose people with Marfan syndrome (Wright 2016). As

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participants in Shores 1994 met the diagnostic criteria published by Beighton 1988, now largely considered a joint hypermobility score, it is possible that people without Marfan syndrome may have been included in the study.

Male and female participants in both study groups had greater measured initial aortic diameter than expected values, therefore the results from the study cannot be applied to people without aortic dilatation at the initiation of beta-blocker therapy. Furthermore, as children less than 12 years old were excluded, the outcomes can only be generalised to the adolescent and adult population although the study authors suggest earlier treatment provides greater benefit.

Quality of the evidence

Although the single included study is a RCT, which is considered the highest-quality study design, we judged the evidence to be of low quality using the GRADE approach for all outcomes. The single included study was at high risk of selection (allocation concealment), performance, detection, attrition and selective reporting bias. Additionally, we further downgraded the evidence because we judged imprecision to be serious, due to very wide confidence intervals for all outcome measures.

With the exception of mortality and aortic diameter, most other primary as well as secondary clinically relevant outcomes identified in this review were not adequately reported in the published manuscript. In this study when participants reached a pre-defined end point, they were withdrawn from the trial and their follow-up data were not reported. Adverse events data were poorly documented and therefore we could not evaluate the benefits versus harm of long-term beta-blocker therapy.

Since we judged the single trial to be of low quality, our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect. This study provides inadequate evidence to inform people with Marfan syndrome, and their families and care-providers.

Potential biases in the review process

We performed a comprehensive literature search to identify all studies meeting the inclusion criteria from several databases. We did not limit our search to a particular language and we followed strictly the methodology described in the published protocol.

Only one randomised trial met the inclusion criteria, therefore study findings have not been replicated. It was not possible to collect all relevant information for the pre-defined outcomes outlined in this review as they were not reported in the published study. However, we successfully contacted the study authors and obtained additional information.

Agreements and disagreements with other studies or reviews

The present study is the only RCT that compares beta-blocker therapy with no treatment in Marfan syndrome. Although RCTs are considered the highest level of evidence, we recognise that data are available from non-randomised studies on beta-blocker monotherapy in Marfan syndrome and provide valuable information.

Several retrospective and prospective studies evaluating the efficacy of beta-blocker therapy have demonstrated conflicting results and we have summarised these in Additional Table 4.

Beta-blocker compared to no treatment

The non-randomised, retrospective studies by Ladouceur 2007 and Salim 1994 analysed the effect of beta-blockade on aortic dilatation in participants with Marfan's syndrome. Although Ladoceur and colleagues focused on a paediatric sub-population (mean age at diagnosis: 6.7 years) and Salim and colleagues included an older, adolescent sub-population less than 21 years of age, both studies reported that beta-blocker therapy reduced the rate of aortic dilatation. We note that Salim 1994 had a small number of participants in the control group (N = 13), composed of patients who could not or would not take beta-blockade therapy, compared to the beta-blocker treatment group (N = 100). Beta-blockers used in both studies were atenolol, nadolol and propranolol. In contrast, another retrospective study, Tierney 2007, demonstrated no significant difference between beta-blocker therapy and no treatment over a six- to seven-year follow-up in a population less than 18 years old. Additionally there was no significant difference in clinical endpoints reached or adverse symptoms reported. Although specific exercise testing was not routinely used to assess optimal beta-blockade dosing, the study authors report that the heart rate and heart rate z-scores were significantly lower in the treatment group at the time of last follow-up.

We identified two prospective studies assessing beta-blocker mono-therapy compared to no treatment (Rossi-Foulkes 1999; Tahernia 1993). Tahernia 1993 was a small study of six participants that reported that people with Marfan's syndrome (N = 3) taking beta-blockade therapy had no progression of aortic root dilatation. Rossi-Foulkes 1999, a non-randomised, prospective study compared treatment with beta-blocker or calcium channel blocker with no treatment in children with Marfan syndrome and reported a beneficial impact of drug therapy on the absolute and relative rates of aortic root growth.

Legget 1996 and Silverman 1995 were two retrospective studies. Although their primary endpoints did not include measuring the effects of beta-blocker therapy in Marfan's syndrome, they did include a subanalysis of the efficacy of beta-blocker treatment in their published reports. Silverman 1995, a large retrospective, multi-centre study of 417 participants with Marfan's syndrome evaluating life-expectancy in this population suggested that the 119 participants on a wide variety of types and dosages of beta-blocker therapy conferred benefit for survival. The study did not report on aortic root changes. Legget 1996 studied various clinical and echocardiographic predictors of outcome in Marfan's syndrome and reported no change in aortic ratio between beta-blocker therapy (N = 30) and no therapy (defined as never received or received for less than one year, N = 53), over a mean follow-up of four years.

Though the above studies suggest agreement with the included Shores 1994 RCT in this review that beta-blockers may decrease the rate of aortic dilatation, these studies must be interpreted with caution given their limitations, differences in study design and high risk of bias.

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Beta-blocker compared to other anti-hypertensives

The data comparing beta-blocker therapy to other anti-hypertensives are more robust. Although our review focus is beta-blocker monotherapy, for the reasons outlined in the introduction, we provide a brief summary and outline of the literature below and in Table 5. We excluded the RCTs listed in this table from our review as they did not include a no-treatment control group.

Phomakay 2014 was a retrospective study of 67 people, comparing the effects of beta-blockers versus ACE inhibitors versus no treatment on aortic root growth rate in Marfan syndrome for an average of 7.6 years. A normal control group was also included. Beta-blockers used were atenolol, metoprolol and propranolol, while the ACE inhibitors were lisinopril, enalapril and captopril. They reported that beta-blocker therapy resulted in near normalisation of aortic growth velocity (AGV), while ACE inhibitors did not significantly attenuate AGV. Two participants experienced aortic dissections, one from the beta-blocker group and the other from the ACE-inhibitor group. In contrast, Yetman 2005, a prospective, non-randomised trial assessing the effects of enalapril compared to beta-blocker therapy in 57 participants over three years demonstrated that enalapril was superior to beta-blocker in improving aortic distensibility and stiffness, with associated slower rate of aortic growth. Additionally, the study authors reported an increased number of adverse effects and participants undergoing aortic root replacement from the beta-blocker group. One death occurred in the beta-blocker group with documented ventricular tachyarrhythmia.

Three small and relatively short RCTs (Bhatt 2015; Sandor 2015; Williams 2012) evaluated the haemodynamic and biophysical aortic effects of pharmacological therapy in Marfan's syndrome. Williams 2012 assessed the efficacy of atenolol, perindopril and verapamil in 18 participants with a mean age of 30.4 years and reported that all drug groups reduced peripheral and central pressure. Atenolol further delayed aortic wave travel. No significant change in aortic diameter was observed over 18 weeks of follow-up. Bhatt 2015 and Sandor 2015 both compared the effects of losartan and atenolol and although they reported differing effects of atenolol on pulse wave velocity, concluded that atenolol and losartan had different mechanisms of action on aortic function, indicating a role for both in the treatment for Marfan's syndrome. Neither study reported a significant change in aortic root dilatation for either treatment group over a study duration of 6 to 12 months.

Two RCTs (Forteza 2016; Lacro 2014) have recently been published, comparing the effects of losartan and atenolol over a three-year period. Neither had a no-treatment control group. Lacro 2014 recruited 604 participants distributed between 21 clinical centres and found no significant difference in the rate of aortic root dilatation between losartan and beta-blocker treatment in children and young adults (age range: 6 to 25 years). They reported a possible higher rate of adverse events in participants treated with beta-blockade, but there was no difference in adverse clinical outcomes between the two groups. Similarly, Forteza 2016, a randomised, parallel, double-blind study reported no significant difference in the progression of aortic root and ascending aortic diameters between losartan and atenolol. Further, they demonstrated that aortic root diameter increased significantly in both groups. No serious adverse effects were observed in either treatment group.

Comparison with other reviews

Two meta-analyses have been conducted on the efficacy of beta-blocker therapy versus no treatment in people with Marfan syndrome (Gao 2011; Gersony 2007).

1. Gao 2011 focused on a subpopulation of children and adolescents with Marfan syndrome and included five non-randomised studies (Ladouceur 2007; Rossi-Foulkes 1999; Salim 1994; Tahernia 1993; Tierney 2007) to assess the effectiveness of beta-blocker therapy on aortic dilatation and clinical outcomes (death, cardiovascular surgery, aortic dissection or rupture). Out of a study population of 392 children and adolescents less than 18 years old, their meta-analysis reported a significantly decreased rate of aortic dilatation with treatment (SMD -1.30, 95% CI -2.11 to -0.49, P = 0.002). There was no significant difference in clinically important endpoints (death, cardiovascular surgery, or aortic dissection or rupture). Beta-blockers used were mainly atenolol or propranolol. The authors acknowledge an important limitation of their analysis in that the measured aortic change was not normalised to body size as these data were not reported in their selected studies. However, they recognise that adiposity is often reduced in their young study population and state that reporting on absolute diameter is appropriate.
2. In contrast, Gersony 2007 report from their meta-analysis that there is no evidence of clinical benefit from long-term beta-blockade in people with Marfan syndrome. Their analysis imposed no restriction on age and included six studies, one of which was the RCT included in this review (Shores 1994), two non-randomised, prospective studies, and three studies that were not designed to observe the effect of beta-blocker therapy. Clinical endpoints were defined as aortic dissection or rupture, cardiovascular surgery or death. Aortic root dimensions were not included in the analysis. Beta-blockers included in the studies were mainly atenolol and propranolol, but one study (Silverman 1995) additionally included nadolol and metoprolol. Out of 433 participants in the treatment group and 369 participants in the untreated group, participants on beta-blocker therapy were more likely to reach a clinical endpoint using a fixed-effects model (odds ratio (OR) 1.50, 95% CI 1.05 to 2.16). However, when a random-effects model was applied, no statistical significance was reached for treatment effect (OR 1.54, 95% CI 0.99 to 2.40). The authors acknowledge that the length of time on beta-blocker treatment was not included in three selected studies and the presence or non-presence of advanced aortic disease was not included in the analysis.

These two meta-analyses report contradicting conclusions on the efficacy of beta-blocker therapy but they are both limited by the heterogeneous design of the included studies and the combination of randomised and non-randomised data. Gao 2011's conclusion that beta-blocker therapy can significantly slow the progression of aortic dilatation is in keeping with our single included RCT.

A recent review by Singh 2016 provides a comprehensive summary on recent clinical drug trials and clinical implications in Marfan syndrome. This publication presents data comparing the various groups of anti-hypertensive medications that have been examined for their prophylactic effectiveness on aortic dilatation including beta-blockers, ARBs with and without baseline beta-blocker therapy, and ACE inhibitors. The report concludes that medical therapy in Marfan syndrome should be individualised according to

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patient tolerance and various risk factors including age and family history of aortic dissection. The authors of Singh 2016 recommend that those with aortic root dilatation should receive therapy with adequate doses of either a beta-blocker or ARB, and if severe, a combination of these therapies should be considered. They state that the evidence for prophylactic medication in people without aortic dilatation is less clear.

In summary, the above comparisons with other identified studies and reviews are suggestive that beta-blocker therapy may decrease the rate of aortic root dilatation in Marfan syndrome. However, our review specifically sought to examine the effect of beta-blockers in the prevention of aortic dissection, the significant contributor to morbidity and mortality in this disease, and this outcome along with additional clinical adverse events remain inadequately addressed.

AUTHORS' CONCLUSIONS

Implications for practice

From the one randomised controlled trial (RCT) that met the inclusion criteria for this review, we found very low-quality evidence that beta-blockers decrease the rate of aortic dilatation in the adolescent and adult population with Marfan syndrome. This means that we have very little confidence in the effect estimate and it is likely to be substantially different from the true effect. We believe the evidence is too poor to inform patients on clinical outcomes. The decrease in aortic diameter did not lead to reduced mortality, and non-fatal morbidity outcomes were not different between treatment and control groups. It is therefore difficult to know the clinical relevance of the small but statistically significant decreased rate of aortic root growth and whether the reduced rate of aortic dilatation confers benefit on prognosis. We therefore cannot make definitive conclusions on the efficacy of beta-blocker treatment on overall and event-free survival, quality of life or adverse effects of this potentially life-long treatment.

Implications for research

This review has highlighted the limited evidence that supports the role of beta-blockers as a gold-standard, prophylactic treatment in people of all ages with Marfan's syndrome. High-quality RCTs are required to establish more robust recommendations. However, this will be challenging as it may be considered unethical to conduct a double-blind, placebo study given that beta-blockers have been demonstrated to reduce the rate of aortic dilatation and the potentially fatal nature of aortic dissection and other cardiovascular outcomes in Marfan's syndrome. If such future trials were conducted, it would likely only be feasible with an open-label control or if aortic dilatation was not present at study initiation – a subpopulation where the role of beta-blocker treatment is even more controversial. Close surveillance and well-defined clinical endpoints would be important in the study design. Furthermore, future studies will need to incorporate clinically relevant outcome measures, such as mortality, non-fatal serious endpoints such as aortic dissection and cardiovascular surgery, quality of life and adverse events. Subanalyses according to age, sex, pregnancy, family history, genetic mutation, drug subtype and dosing would provide valuable insight. The effectiveness of other non-pharmacological interventions such as lifestyle, exercise, frequency and type of surveillance also warrants further research.

Given that beta-blockers have now become the accepted norm in clinical practice and it is therefore unlikely that new studies with beta-blocker monotherapy will be conducted in the future, we would like to expand the scope of this review in future updates and systematically review all available information including other study designs such as non-randomised clinical trials and retrospective studies.

Lastly, the focus of our review is on beta-blocker monotherapy compared to no treatment or surveillance only. Further review on the comparison with other anti-hypertensive medications and the role of combination therapy with beta-blockers is required.

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REFERENCES

References to studies included in this review

Shores 1994 *{published data only}*

Shores J, Berger KR, Murphy EA, Pyeritz RE. Progression of aortic dilatation and the benefit of long term beta-adrenergic blockade in Marfan's syndrome. *New England Journal of Medicine* 1994;**330**(9):1335-41.

References to studies excluded from this review

Bhatt 2015 *{published data only}*

Bhatt AB, Buck JS, Zuflacht JP, Milian J, Kadivar S, Guavreau K, et al. Distinct effects of losartan and atenolol on vascular stiffness in Marfan syndrome. *Vascular Medicine* 2015;**20**:317-25.

Forteza 2016 *{published data only}*

Forteza A, Evangelista A, Sanchez V, Teixido-Tura G, Sanz P, Gutierrez L, et al. Efficacy of losartan vs. atenolol for the prevention of aortic dilation in Marfan syndrome: a randomized clinical trial. *European Heart Journal* 2016;**37**:978-85.

Lacro 2014 *{published data only}*

Lacro RV, Dietz HC, Sleeper LA, Yetman AT, Bradley TJ, Colan SD, et al. Atenolol versus losartan in children and young adults with Marfan's syndrome. *New England Journal of Medicine* 2014;**371**:2061-71.

Sandor 2015 *{published data only}*

Sandor GGS, Alghamdi MH, Raggin LA, Potts MT, Williams LD, Potts JE, et al. A randomized, double blind pilot study to assess the effects of losartan vs atenolol on the biophysical properties of the aorta in patients with Marfan and Loeys-Dietz syndromes. *International Journal of Cardiology* 2015;**179**:470-5.

Williams 2012 *{published data only}*

Williams A, Kenny D, Wilson D, Fagenello G, Nelson M, Dunstan F, et al. Effects of atenolol, perindopril and verapamil on haemodynamic and vascular function in Marfan syndrome - a randomised, double-blind, crossover trial. *European Journal of Clinical Investigation* 2012;**42**(8):891-99.

Additional references

Beighton 1988

Beighton P, de Paepe A, Danks D, Finidori G, Gedde-Dahl T, Goodman R, et al. International nosology of heritable disorders of connective tissue, Berlin, 1986. *American Journal of Medical Genetics* 1988;**29**:581-94.

Belz 1995

Belz GG. Elastic properties and Windkessel function of the human aorta. *Cardiovascular Drugs and Therapy* 1995;**9**:73-83.

Boodhwani 2014

Boodhwani M, Andelfinger G, Leipsic J, Lindsay T, McMurty MS, Therrien J, et al. Canadian Cardiovascular Society position statement on the management of thoracic aortic disease. *Canadian Journal of Cardiology* 2014;**30**:577-89.

Bunton 2001

Bunton TE, Biery NJ, Myers L, Gayraud B, Ramirez F, Dietz HC. Phenotypic alteration of vascular smooth muscle cells precedes elastolysis in a mouse model of Marfan syndrome. *Circulation Research* 2001;**88**(1):37-43.

Canadas 2010

Canadas V, Vilacosta I, Bruna I, Fuster V. Marfan syndrome. Part 2: treatment and management of patients. *Nature Reviews. Cardiology* 2010;**7**(5):266-76.

Castellano 2012

Castellano JM, Kovacic JC, Sanz J, Fuster V. Are we ignoring the dilated thoracic aorta?. *Annals of the New York Academy of Sciences* 2012;**1254**:164-74.

Danyi 2011

Danyi P, Elefteriades JA, Jovin IS. Medical therapy of thoracic aortic aneurysms. Are we there yet?. *Circulation* 2011;**124**:1469-76.

Danyi 2012

Danyi P, Elefteriades JA, Jovin IS. Medical therapy of thoracic aortic aneurysms. *Trends in Cardiovascular Medicine* 2012;**22**:180-4.

De Paepe 1996

De Paepe A, Devereux RB, Dietz HC, Hennekam RC, Pyeritz RE. Revised diagnostic criteria for the Marfan syndrome. *American Journal of Medical Genetics* 1996;**62**(4):417.

Deeks 2011

Deeks JJ, Higgins JPT, Altman DG (editors). Chapter 9: Analysing data and undertaking meta-analyses. In: Higgins JPT, Green S (editors). Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0 (updated March 2011). The Cochrane Collaboration, 2011. Available from www.handbook.cochrane.org.

Franken 2012

Franken R, Den Hartog AW, Singh M, Pals G, Zwinderman AH, Groenink M, et al. Marfan syndrome: progress report. *Progress in Pediatric Cardiology* 2012;**34**:9-14.

Gambarin 2009

Gambarin F, Favalli V, Serio A, Regazzi M, Pasotti M, Klersy C, et al. Rationale and design of a trial evaluating the effects of losartan vs. nebivolol vs. the association of both on the progression of aortic root dilation in Marfan syndrome with FBN1 gene mutations. *Journal of Cardiovascular Medicine* 2009;**10**(4):354-62.

Gao 2011

Gao L, Mao Q, Wen D, Zhang L, Zhou X, Hui R. The effect of beta-blocker therapy on progressive aortic dilatation in children and adolescents with Marfan's syndrome: a meta-analysis. *Acta Paediatrica* 2011;**100**:101-5.

Copyright © 2017 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

Gersony 2007

Gersony DR, McClaughlin MR, Jin Z, Gersony WM. The effect of beta-blocker therapy on clinical outcome in patients with Marfan's syndrome: a meta-analysis. *International Journal of Cardiology* 2007;**114**:303-8.

Groenink 1998

Groenink M, De Roos A, Mulder BJM, Spaan JAE, Van der Wall EE. Changes in aortic distensibility and pulse wave velocity assessed with magnetic resonance imaging following beta-blocker therapy in the Marfan syndrome. *American Journal of Cardiology* 1998;**82**:203-8.

Halpern 1971

Halpern BL, Char F, Murdoch JL, Horton WB, McKusick VA. A prospectus on the prevention of aortic rupture in the Marfan syndrome with data on survivorship without treatment. *Johns Hopkins Medical Journal* 1971;**129**:123-9.

Higgins 2003

Higgins JPT, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. *BMJ* 2003;**327**:557-60.

Higgins 2011

Higgins JPT, Altman DG, Sterne JAC (editors). Chapter 8: Assessing risk of bias in included studies. In: Higgins JPT, Green S (editors). Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0 (updated March 2011). The Cochrane Collaboration, 2011. Available from handbook.cochrane.org.

Hirata 1991

Hirata K, Triposkiadis F, Sparks E, Bowen J, Wooley CF, Boudoulas H. The Marfan syndrome: abnormal aortic elastic properties. *Journal of the American College of Cardiology* 1991;**181**(1):57-63.

Hiratzka 2010

Hiratzka LF, Bakris GL, Beckman JA, Bersin RM, Carr VF, Casey Jr DE, et al. 2010 ACCF/AHA/AATS/ACR/ASA/SCA/SCAI/SIR/STS/SVM guidelines for the diagnosis and management of patients with thoracic aortic disease: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines, American Association for Thoracic Surgery, American College of Radiology, American Stroke Association, Society of Cardiovascular Anesthesiologists, Society for Cardiovascular Angiography and Interventions, Society of Interventional Radiology, Society of Thoracic Surgeons, and Society for Vascular Medicine. *Circulation* 2010;**121**:266-369.

Judge 2005

Judge DP, Dietz HC. Marfan's syndrome. *Lancet* 2005;**366**:1965-76.

Keane 2008

Keane MG, Pyeritz RE. Medical management of Marfan syndrome. *Circulation* 2008;**117**:2802-13.

Koracevic 2012

Koracevic G, Sakac D, Pavlovic M, Ilic D, Tomasevic M, Kostic T. Should we prescribe "vasodilating" beta-blockers in Marfan syndrome to prevent aortic aneurysm and dissection?. *Vojnosanitetski Pregled. Military-Medical and Pharmaceutical Review* 2012;**69**(2):195-200.

Ladouceur 2007

Ladouceur M, Fermanian C, Lupoglazoff JM, Edouard T, Dulac Y, Acar P, et al. Effect of beta blockade on ascending aortic dilatation in children with the Marfan syndrome. *American Journal of Cardiology* 2007;**99**:406-9.

Lefebvre 2011

Lefebvre C, Manheimer E, Glanville J. Chapter 6: Searching for studies. In Higgins JPT, Green S (editors). Cochrane Handbook for Systematic Review of Interventions Version 5.1.0. (updated March 2011). The Cochrane Collaboration, 2011. Available from handbook.cochrane.org.

Legget 1996

Legget ME, Unger TA, O'Sullivan CK, Zwink TR, Bennett RL, Byers PH, et al. Aortic root complications in Marfan's syndrome: identification of a lower risk group. *Heart* 1996;**75**:389-95.

Liao 2010

Liao SL, Elmariah S, Van der Zee S, Sealove BA, Fuster V. Does medical therapy for thoracic aortic aneurysms really work? Are beta-blockers truly indicated?. *Cardiology Clinics* 2010;**28**:261-9.

Loeys 2010

Loeys BL, Dietz HC, Braverman AC, Callewaert BL, De Backer J, Devereux RB, et al. The revised Ghent nosology for the Marfan syndrome. *Journal of Medical Genetics* 2010;**47**(7):476-85.

Loke 2011

Loke YK, Price D, Herxheimber A. Chapter 14: Adverse effects. In: Higgins JPT, Green S (editors), Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0 (updated March 2011). The Cochrane Collaboration, 2011. Available from handbook.cochrane.org.

McKusick 2004

McKusick VA. Historical introduction. The Marfan syndrome: from clinical delineation to mutational characterization, a semiautobiographic account. In: Robinson PN, Godfrey M editor(s). Marfan Syndrome: a Primer for Clinicans and Scientists. Dordrecht, the Netherlands: Eurekah.com and Kluwer Academic/Plenum Publishers, 2004:1-12.

Milleron 2015

Milleron O, Arnoult F, Ropers J, Aegerter P, Detaint D, Delorme G, et al. Marfan Sartan: a randomized, double-blind, placebo-controlled trial. *European Heart Journal* 2015;**36**:2160-6.

Moberg 2012

Moberg K, De Nobele S, Devos D, Goetghebeur E, Segers P, Trachet B. The Ghent Marfan Trial - a randomized, double-blind placebo controlled trial with losartan in Marfan patients treated with β-blockers. *International Journal of Cardiology* 2012;**157**:354-8.

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Moher 2009

Moher D, Liberati A, Tetzlaff J, Altman DG, the PRISMA Group. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *PLoS Medicine* 2009;**6**(7):e1000100. [DOI: 10.1371/journal.pmed.1000100]

Mullen 2013

Mullen MJ, Flather MD, Jin XY, Newman WG, Erderm G, Gaze D, et al. A prospective, randomized, placebo-controlled, double-blind, multicenter study of the effects of irbesartan on aortic dilatation in Marfan syndrome (AIMS trial): study protocol. *Trials* 2013;**14**:1-14.

Murdoch 1972

Murdoch JL, Walker BA, Halpern BL, Kuzma JW, McKusick VA. Life expectancy and causes of death in the Marfan syndrome. *New England Journal of Medicine* 1972;**286**:804-8.

Phomakay 2014

Phomakay V, Huett WG, Gossett JM, Tang X, Bornemeier RA, Collins RT. β-Blockers and angiotensin converting enzyme inhibitors: comparison of effects on aortic growth in pediatric patients with Marfan syndrome. *Journal of Pediatrics* 2014;**165**:951-5.

Pitcher 2015

Pitcher A, Emberson J, Lacro RV, Sleeper LA, Stylianou M, Mahony L, et al. Design and rationale of a prospective, collaborative meta-analysis of all randomized controlled trials of angiotensin receptor antagonists in Marfan syndrome, based on individual patient data: a report from the Marfan Treatment Trialists' Collaboration. *American Heart Journal* 2015;**169**:605-12.

Pyeritz 2000

Pyeritz RE. The Marfan syndrome. *Annual Review of Medicine* 2000;**51**:481-510.

Pyeritz 2008

Pyeritz RE. A small molecule for a large disease. *New England Journal of Medicine* 2008;**358**:2829-31.

Pyeritz 2009

Pyeritz RE. Marfan syndrome: 30 years of research equals 30 years of additional life expectancy. *Heart (British Cardiac Society)* 2009;**95**(3):173-5.

Pyeritz 2012

Pyeritz RE. Evaluation of the adolescent or adult with some features of Marfan syndrome. *Genetics in Medicine* 2012;**14**:171-7.

Pyeritz 2014

Pyeritz RE. What is the optimal medical therapy for Marfan syndrome?. *Journal of Pediatrics* 2014;**165**:889-90.

RevMan 2014 [Computer program]

Nordic Cochrane Centre, The Cochrane Collaboration. Review Manager 5 (RevMan 5). Version 5.3. Copenhagen: Nordic Cochrane Centre, The Cochrane Collaboration, 2014.

Rios 1999

Rios AS, Silber EN, Bavishi N, Varga P, Burton BK, Clark WA, et al. Effect of long-term β-blockade on aortic root compliance in patients with Marfan syndrome. *American Heart Journal* 1999;**137**:1057-61.

Rossi-Foulkes 1999

Rossi-Foulkes R, Roman MJ, Rosen SE, Kramer-Fox R, Ehlers KH, O'Loughlin JE, et al. Phenotypic features and impact of beta blocker or calcium antagonist therapy on aortic lumen size in the Marfan syndrome. *American Journal of Cardiology* 1999;**83**:1364-68.

Rughani 2012

Rughani G, Robertson L, Clarke M. Medical treatment for small abdominal aortic aneurysms. *Cochrane Database of Systematic Reviews* 2012, Issue 9. [DOI: 10.1002/14651858.CD009536.pub2]

Salim 1994

Salim MA, Alpert BS, Ward JC, Pyeritz RE. Effect of beta-adrenergic blockade on aortic root rate of dilation in the Marfan syndrome. *American Journal of Cardiology* 1994;**74**:629-33.

Selamet Tierney 2007

Selamet Tierney ES, Feingold B, Printz BF, Park SC, Graham D, Kleinman CS, et al. Beta-blocker therapy does not alter the rate of aortic root dilation in pediatric patients with Marfan syndrome. *Journal of Pediatrics* 2007;**150**:77-82.

Silverman 1995

Silverman DI, Burton KJ, Gray J, Bosner MS, Kouchoukos NT, Roman MJ, et al. Life expectancy in the Marfan syndrome. *American Journal of Cardiology* 1995;**75**(2):157-60.

Singh 2016

Singh MN, Lacro RV. Recent clinical drug trials evidence in Marfan syndrome and clinical implications. *Canadian Journal of Cardiology* 2016;**32**:66-77.

Tahernia 1993

Tahernia AD. Cardiovascular anomalies in Marfan's syndrome: the role of echocardiography and b-blockers. *Southern Medical Journal* 1993;**86**:305-10.

Tierney 2007

Tierney ESS, Feingold B, Printz BF, Park SC, Graham D, Kleinman CS, et al. Beta-blocker therapy does not alter the rate of aortic root dilation in pediatric patients with Marfan syndrome. *Journal of Pediatrics* 2007;**150**(1):77-82.

Topouchian 1998

Topouchian J, Brisac AM, Pannier B, Vicaut E, Safar M, Asmar R. Assessment of the acute arterial effects of converting enzyme inhibition in essential hypertension: a double-blind comparative and crossover study. *Journal of Human Hypertension* 1998;**12**:181-7.

Vaidyanathan 2008

Vaidyanathan B. Role of beta-blockers in Marfan's syndrome and bicuspid aortic valve: a time for re-appraisal. *Annals of Pediatric Cardiology* 2008;**1**:149-52.

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Von Kodolitsch 2004

Von Kodolitsch Y, Rybczynski M. Cardiovascular aspects of the Marfan syndrome: a systematic review. In: Robinson PN, Godfrey M editor(s). Marfan Syndrome: a Primer for Clinicans and Scientists. Dordrecht, the Netherlands: Eurekah.com and Kluwer Academic/Plenum Publishers, 2004:45-69.

Von Kodolitsch 2007

Von Kodolitsch Y, Robinson PN. Marfan syndrome: an update of genetics, medical and surgical management. *Heart (British Cardiac Society)* 2007;**93**(6):755-60.

Wright 2012

Wright JM, Connolly HM. Management of Marfan syndrome and related disorders. In: UpToDate, Post TW (Ed), UpToDate, Waltham, MA (Accessed 9 April 2014).

Wright 2016

Wright JM, Connolly HM. Genetics, clinical features, and diagnosis of Marfan syndrome and related disorders. In: UpToDate, Post TW (Ed), UpToDate, Waltham MA (Accessed June 2017).

Yetman 2005

Yetman AT, Bornemeier RA, McCrindle BW. Usefulness of enalapril versus propranolol or atenolol for prevention of aortic dilation in patients with the Marfan syndrome. *American Journal of Cardiology* 2005;**95**:1125-7.

CHARACTERISTICS OF STUDIES

Characteristics of included studies *[ordered by study ID]*

Shores 1994

Methods	**Design**: randomised, open-label trial of long-term beta-adrenergic blockade in Marfan syndrome

Participants	**Population**
	• All participants had been evaluated within 1 year at the Medical Genetics Clinic of the John Hopkins Hospital, USA before enrolment into the study
	• 117 patients were considered, 93 were eligible and invited to participate. 70 (75.3%) patients gave informed consent and were included in the study
	• Participants were randomly assigned to treatment (32) or control (38) for an average duration of 9.3 years in the control group and 10.7 years in the treatment group.
	• Of those excluded, 12 had aortic regurgitation, 5 poor ventricular function, 4 bronchospasm, and 3 atrioventricular conduction delay. 11 of the 23 who declined to participate did so because they lived too far away from the clinic.
	• Patients who were eligible for the study but who chose not to participate did not differ appreciably in any of the characteristics from participants in the treatment and control groups combined.
	Inclusion criteria
	• Adolescent and adult patients aged 12-50 years
	• Diagnosed with classic Marfan syndrome under the internationally established Berlin 1986 diagnostic criteria involving multiple systems: skeletal, ocular, cardiovascular, pulmonary, skin and integument, and the central nervous systems. The classic form was considered if abnormalities of the eye (ectopia lentis), aorta (aneurysm of the ascending aorta and aortic regurgitation), skeleton (dolichostenomelia, arachnodactyly, pectus deformity and mild joint laxity) were present. Requirements for diagnosis were:
	  • In the absence of an unequivocally affected 1° relative: involvement of the skeleton and at least 2 other systems; at least 1 major manifestation
	  • In the presence of at least 1 unequivocally affected 1° relative: involvement of at least 2 systems; at least 1 major manifestation preferred, but this will depend somewhat on the family's phenotype
	  • Urine amino acid analysis in the absence of pyridoxine supplementation confirms absence of homocystinuria
	Exclusion criteria
	• Aged < 12 or > 50 years
	• Receiving ongoing treatment with propranolol

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Shores 1994 *(Continued)*

- Any of the following features: aortic dissection; aortic regurgitation on auscultation; moderate or severe mitral regurgitation; previous cardiovascular surgery; dyspnoea during moderate exercise, orthopnoea, peripheral oedema, left ventricular ejection fraction < 50%; atrioventricular conduction delay of any degree; disorders in which propranolol was contraindicated (diabetes mellitus or recurrent bronchospasm requiring medical treatment).

Baseline characteristics at entry

- Mean age (years): control; 15.4, treatment; 14.5
- Gender (M:F): control; 20:12, treatment; 19:19
- Systolic/diastolic blood pressure with SD (mmHg):
  - Control (M:F): 118/72 ± 14/11: 110/70 ± 13/10
  - Treatment (M:F): 115/73 ± 13/10: 115/69 ± 14/13
- Heart rate: beats/min ± SD
  - Control (M:F): 78 ± 18: 79 ± 17
  - Treatment (M:F): 74 ± 9: 84 ± 14
- Number with mitral valve collapse (M:F): control; 12:14, treatment; 12:10
- Number with mitral regurgitation (M:F): control; 5:5, treatment; 5:7
- Initial measured aortic diameter ± SD (mm)
  - Control (M:F): 31.1 ± 6.9: 29.4 ± 6.8
  - Treatment (M:F): 36.7 ± 9.3: 31.2 ± 5.3
- Systolic time interval
  - Control (M:F): 0.38 ± 0.22: 0.36 ± 0.18
  - Treatment (M:F): 0.39 ± 0.17: 0.35 ± 0.15

Interventions	**Treatment** • Propranolol: initial dose of 10 mg, 4 times/d • Subsequent maintenance dose: individualised according to response of the heart rate to exercise and systolic interval assessed after 2-4 weeks. Propranolol dose was increased until the heart rate remained < 100 beats/min during exercise or the systolic time interval increased by 30% • Mean dose (± standard error) was 212 ± 68 mg daily given in 4 divided doses **Control** • No treatment
Outcomes	Participants remained in the study until 1 of the following endpoints was reached: **Clinical endpoints** • Death • Aortic dissection • Development of aortic regurgitation detectable by auscultation • Cardiovascular surgery • Congestive heart failure (indicated by new-onset dyspnoea, orthopnoea, peripheral edema or fatigability associated with a left ventricular ejection fraction of less than 40%) **Other end points** • Voluntary withdrawal • Intractable adverse reaction to propranolol
Notes	**Follow-up** Participants were evaluated every 6-12 months. History and physical examination, electrocardiography and echocardiography were performed at each visit.

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Shores 1994 *(Continued)*

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "once consent was obtained, a patient was assigned the next available number from a list derived from a table of random numbers at the beginning of the study" Comment: random sequence generation was probably performed
Allocation concealment (selection bias)	High risk	Quote: "a patient with an even number received no treatment (control group), and a patient with an odd number received propranolol (treatment group)" Comment: study author stated that the investigators were aware of treatment allocation (personal communication)
Blinding of participants and personnel (performance bias) All outcomes	High risk	Quote: "no patient or investigator was blinded to the patient's status after assignment to a study group", "administering a placebo and blinding patients to their group assignment would have been impracticable because the physiologic effects of propranolol are distinctive and difficult to mask or to mimic with placebo" Comment: this study was an open-label study and both participants and investigators were aware of study group they were assigned.
Blinding of outcome assessment (detection bias) All outcomes	High risk	Quote: "throughout the study, the investigator interpreting the echo-cardiograms was kept unaware of the identity of the patients and the sequence of multiple tracings", "the series of studies in each patient were interpreted in random order". Comment: although there is low risk for echocardiogram interpretation, the risk of bias is high for other clinical outcomes except mortality as outcome assessor was not blinded.
Incomplete outcome data (attrition bias) All outcomes	High risk	• Withdrawal due to clinical end-points was reported, but not total withdrawals from study • No report of participant follow-up after withdrawal due to end-point (confirmed by study author: personal communication) • Withdrawals from adverse effects not reported • The published report stated that all comparisons included all participants according to the ITT analysis, however, the study author confirmed that no clinically relevant endpoints were collected during the follow-up period of 9.3 years in the control group and 10.7 years in the treatment group, therefore an ITT analysis at the end of follow-up was not performed (personal communication). • The study author stated that there were no missing data and the last observation was carried forward (personal communication)
Selective reporting (reporting bias)	High risk	Quote: “Because the study was neither blinded nor placebo-controlled the patients in the control group were not queried systematically about similar symptoms”. Comment • The study protocol was not available (confirmed by study author: personal communication) • It would appear in the published report that “aortic root > 6 cm” was added as a clinical endpoint in addition to the stated clinical endpoints in the methods section, however, the study author confirmed that this was a pre-determined clinical end-point (personal communication).

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Shores 1994 *(Continued)*

		• Adverse events were not described by type or distinguished by arm in the published report, however, the study author reported that no adverse events occurred in the control group (personal communication).
Other bias	Unclear risk	• This study was supported by grants from the National Institute of Health, the Food and Drug Administration and by the National Marfan Foundation. • The study author confirmed that no power calculation was performed to determine the sample size (personal communication). • We have judged other bias as unclear as findings from this study have not been replicated, as only a single study met the inclusion criteria.

ITT: intention-to-treat

Characteristics of excluded studies *[ordered by study ID]*

Study	Reason for exclusion
Bhatt 2015	Randomised, double-blind trial comparing the effects of losartan and atenolol on vascular stiffness in Marfan syndrome. No control/placebo group was studied. Study duration was less than one year (6 months).
Forteza 2016	RCT investigating the efficacy of losartan vs. atenolol for the prevention of aortic dilatation in Marfan syndrome. No control/placebo group was studied.
Lacro 2014	RCT comparing losartan with atenolol in children and young adults with Marfan syndrome. No control/placebo group was studied.
Sandor 2015	A randomised, double-blind pilot study assessing the effects of losartan vs atenolol on the biophysical properties of the aorta in people with Marfan and Loeys-Dietz syndromes. No control/placebo group was studied.
Williams 2012	Randomised, double-blind, cross-over trial investigating the effects of atenolol, perindopril and verapamil on haemodynamic and vascular function in Marfan syndrome. No control/placebo group was studied. Total study duration < 1 year (18 weeks)

DATA AND ANALYSES

Comparison 1. Beta-blocker versus no treatment

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 All-cause mortality	1	70	Risk Ratio (M-H, Fixed, 95% CI)	0.24 [0.01, 4.75]
2 Clinically important non-fatal endpoints as defined by Shores 1994	1	70	Risk Ratio (M-H, Fixed, 95% CI)	0.79 [0.37, 1.69]
3 Acute aortic dissection	1	70	Risk Ratio (M-H, Fixed, 95% CI)	0.59 [0.12, 3.03]
4 Aortic regurgitation	1	70	Risk Ratio (M-H, Fixed, 95% CI)	1.19 [0.18, 7.96]

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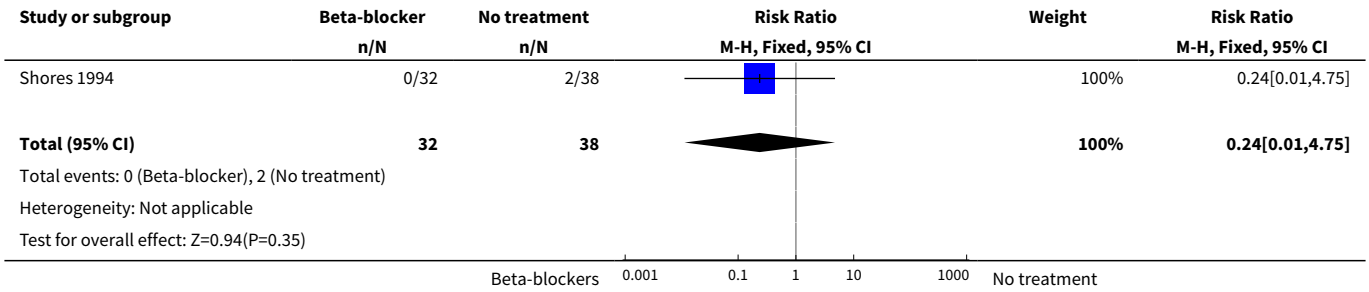
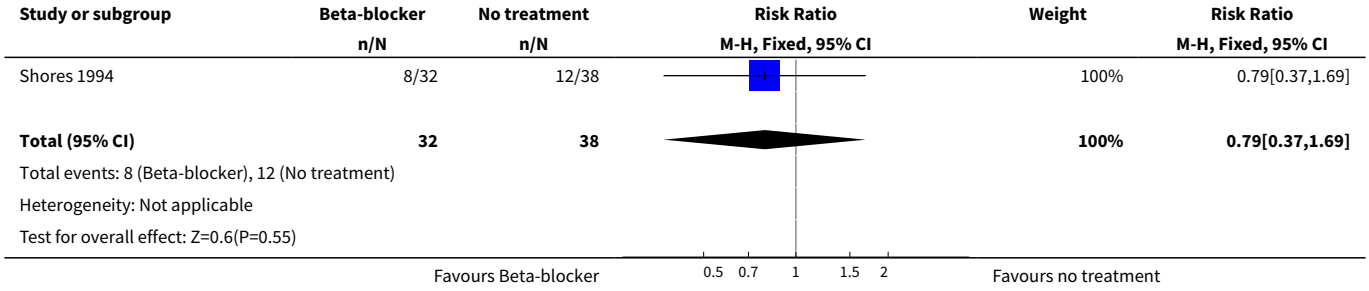
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
5 Congestive heart failure	1	70	Risk Ratio (M-H, Fixed, 95% CI)	1.19 [0.18, 7.96]
6 Cardiovascular surgery	1	70	Risk Ratio (M-H, Fixed, 95% CI)	0.59 [0.12, 3.03]
7 Aortic root diameter > 6 cm	1	70	Risk Ratio (M-H, Fixed, 95% CI)	1.19 [0.08, 18.24]

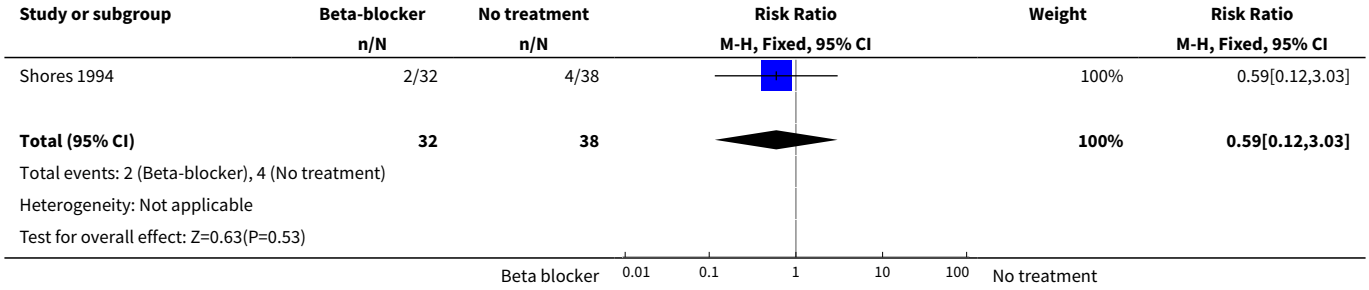
Analysis 1.1. Comparison 1 Beta-blocker versus no treatment, Outcome 1 All-cause mortality.



Analysis 1.2. Comparison 1 Beta-blocker versus no treatment, Outcome 2 Clinically important non-fatal endpoints as defined by Shores 1994.



Analysis 1.3. Comparison 1 Beta-blocker versus no treatment, Outcome 3 Acute aortic dissection.



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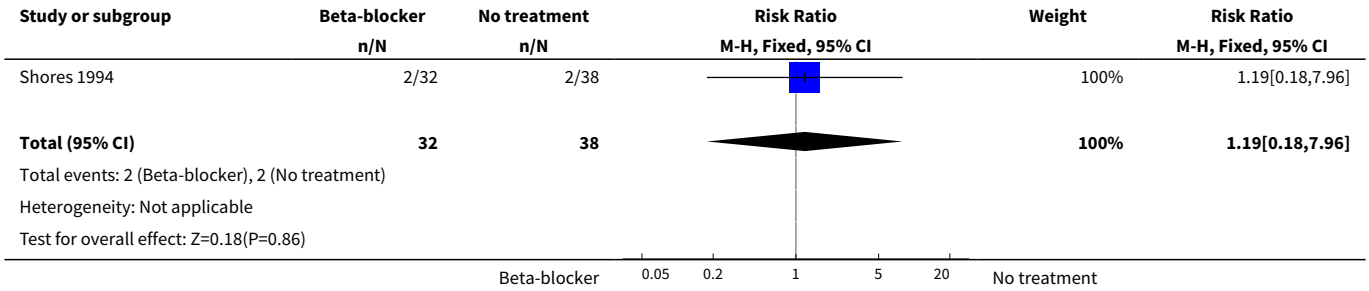
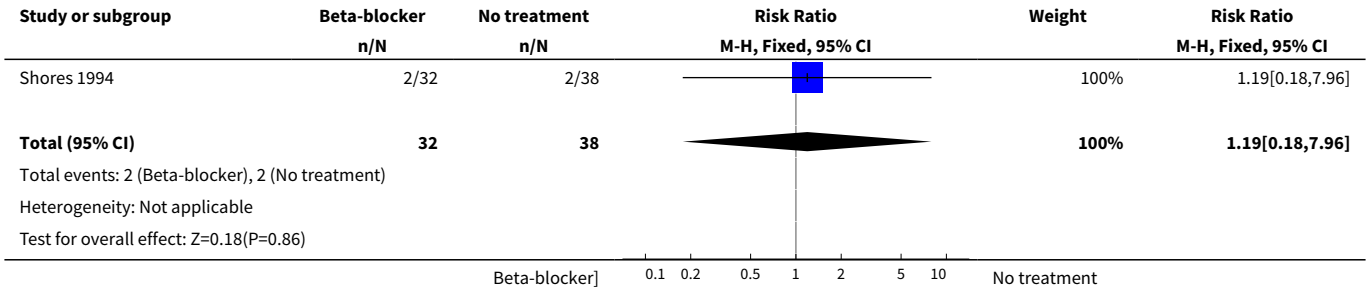
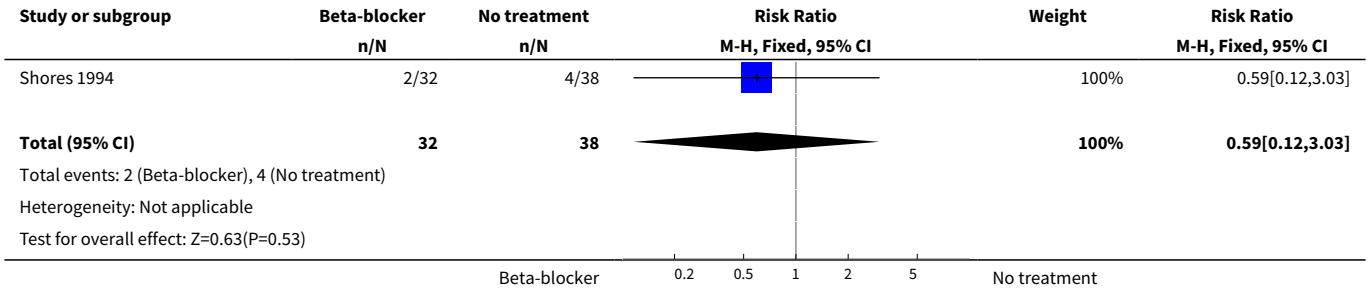
Analysis 1.4. Comparison 1 Beta-blocker versus no treatment, Outcome 4 Aortic regurgitation.



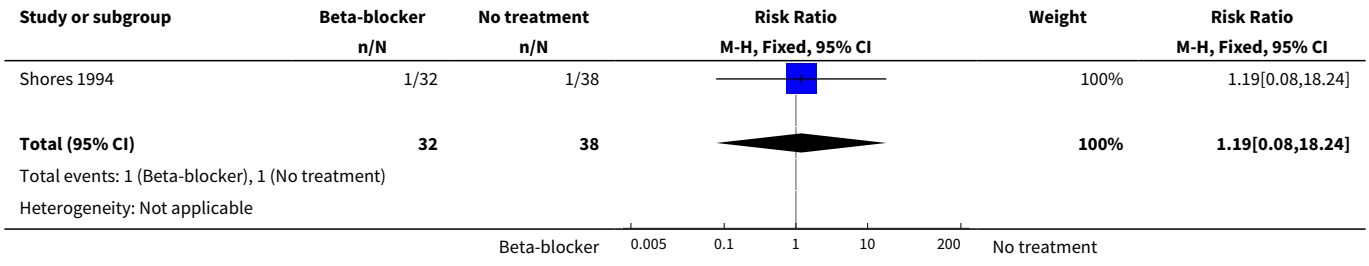
Analysis 1.5. Comparison 1 Beta-blocker versus no treatment, Outcome 5 Congestive heart failure.



Analysis 1.6. Comparison 1 Beta-blocker versus no treatment, Outcome 6 Cardiovascular surgery.



Analysis 1.7. Comparison 1 Beta-blocker versus no treatment, Outcome 7 Aortic root diameter > 6 cm.



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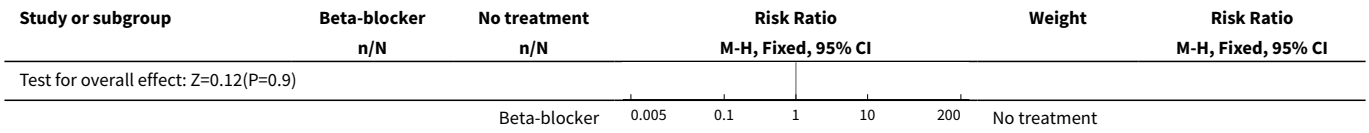

ADDITIONAL TABLES

Table 1. Initial aortic diameter and ratio reported at baseline

Initial aortic diameter	Control male (N = 19)	Control female (N = 19)	Treatment male (N = 20)	Treatment female (N = 12)
Measured (mm) ± SD	31.1 ± 6.9	29.4 ± 6.8	36.7 ± 9.3	31.2 ± 5.3
Expected (mm) ± SD	24.6 ± 3.9	23.3 ± 3.2	25.5 ± 4.1	23.3 ± 4.2
Ratio	1.27 ± 0.19	1.27 ± 0.26	1.43 ±0.26	1.37 ± 0.2

SD: standard deviation

Table 2. Blood pressure measured at baseline and during optimal dose

BP measured as mmHg ±SD	Control male (N = 19)	Control female (N = 19)	Treatment male (N = 20)	Treatment female (N = 12)
SBP at baseline	118 ± 14	110 ± 13	115 ± 13	115 ± 14
DBP at baseline	72 ± 11	70 ± 10	73 ± 10	69 ± 13
SBP during optimal dose	Not reported	Not reported	108 ± 15	108 ± 8
DBP during optimal dose	Not reported	Not reported	66 ± 11	63 ± 7
End of treatment	Not reported	Not reported	Not reported	Not reported

BP: blood pressure; DBP: diastolic blood pressure; SBP: systolic blood pressure

Table 3. Adverse effects of long-term treatment for 30 participants complying with beta-blocker therapy

Adverse effect	Beta-blocker group (N = 30)	Control
Third-degree heart block	1	Not reported in Shores 1994, however, the study author reported that no adverse events occurred in the control group (personal communication)
First-degree heart block	3	
Lethargy	8	
Depression	1	
Insomina	4	

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Table 3. Adverse effects of long-term treatment for 30 participants complying with beta-blocker therapy *(Continued)*

Dream disturbance	3
Mild bronchospasm	1
Accentuated effects of alcohol	1
Total with one or more effects	**10**

Table 4. Additional retrospective and prospective studies evaluating beta-blocker therapy versus no treatment

Study	Study design	Study population	Results	Conclusions
Ladouceur 2007	• Retrospective, multicentre study evaluating the evolution of aortic diameter in children with Marfan syndrome, receiving beta-blocker initiated before 12 years of age (N = 77) compared to no treatment (N = 78) • Beta blockers: atenolol (70%), nadolol (17%) and propranolol (6%) • Treatment was initiated according to physician's practice: at diagnosis or documentation of aortic root dilatation. • Aortic diameters were measured annually by echocardiography • Follow up: < 5 years	• 155 children (82 boys, 73 girls) from 3 outpatient clinics in France • < 12 years at diagnosis • Mean age at diagnosis in years: 6.1 ± 3.2 (treatment), 7.4 ± 5.2 (no treatment)	• 2 study groups were similar in age, height, weight, BP and heart rate at the time of diagnosis • Aortic root dilatation was more frequent in the treatment group. • Beta-blocker therapy was started at an average of 1.3 years after diagnosis in the treatment group (mean age 7.5 ± 3.2 years). • 4 participants died in total (3 sudden deaths, 1 respiratory distress): 3 were from the control group • 2 of 77 children taking beta-blockers stopped treatment during the study • Adverse effects were not reported	• Beta-blockade significantly decreased the rate of aortic dilatation by a mean of 0.16 mm/year compared with untreated participants (P = 0.0383) • Very few mortality and morbidity events prevent further interpretation regarding the potential for harm. • The study authors recommend treatment as soon as the diagnosis is made
Legget 1996	• Purpose of this study was to examine clinical and echocardiographic predictors of outcome in Marfan syndrome (N = 83) • Follow-up: mean = 4 years, range = < 1-16 years	• 36% participants received beta-blocker treatment for > 1 year, 64% never received or received for < 1 year	• Aortic ratios and the change in ratio between initial and final echocardiograms did not differ between the beta-blocker and no-beta-blocker groups • 58 participants on beta-blocker treatment reached a clinical event (defined as death or surgery for ascending aortic dissection or aneurysm) while 37 did not. Those who reached an event were on beta-blocker therapy for a mean of 40 months compared to 20 months in those who didn't have a clinical event.	• Actuarial freedom from all events was no different in those receiving beta-blockers compared with those not receiving beta-blockers at 5 years • The study authors state the limitations of their study make interpretation of the data pertaining to beta-blocker treatment difficult. • A low-risk subgroup of people with Marfan syndrome can be identified as those with aortic ratio < 1.3 and annual change in aortic ratio < 5%

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Table 4. Additional retrospective and prospective studies evaluating beta-blocker therapy versus no treatment *(Continued)*

Phomakay 2014	• Retrospective, single-centre study comparing the effect of beta-blockers vs ACE-inhibitors vs no treatment on aortic root growth rate in people with Marfan syndrome. A normal control group was also included. • Pharmacological choice was provider-dependent and initiated based on aortic measurements or accelerated dilatation. • Beta blockers: atenolol (45.9%), metoprolol (48.5%), propranolol (5.6%) • ACEI: daily lisinopril (12.9%), enalapril (85.5%), captopril (1.6%) • Aortic measurements performed by echocardiography • Mean follow-up: 7.6 ± 5.8 years	• 67 participants with confirmed Marfan syndrome (34 female, 33 male) • Mean age at first encounter: 13 ± 10 years • Mean age for untreated group: 9.8 years, beta-blocker therapy: 16.9 years, ACEI: 16.8 years	• Beta-blocker group had significantly lower heart rate but no difference in BP compared to untreated group. • ACE inhibitor group had significantly higher BP compared to beta-blocker and untreated group. The heart rate was lower compared to the untreated group, but no difference compared to the beta-blocker group. • AGV was significantly attenuated in the beta-blocker group. • Total of 1 participant died; study group not specified • Total of 14 participants underwent surgeries (aortic root replacement in 11/14; median age 17 years). • 2 participants experienced aortic dissections: 1 from the beta-blocker group, 1 from ACEI group	• Beta-blocker therapy resulted in near normalisation of AGV • ACEI did not significantly decrease AGV • The study authors suggest early introduction of beta-blocker therapy should be considered even prior to the demonstration of aortic dilatation.
Rossi-Foulkes 1999	• Prospective, non-randomised, non-blinded study. • Treatment (N = 27): beta-blockers in most participants, verapamil in 1 Verapamil with asthma • No treatment (N = 15) • Dosage was adjusted to achieve maximally tolerated decrease in heart rate and BP • Aortic measurements by echocardiography • Follow-up: 44 ± 24 months	• 43 children (28 boys, 25 girls) with Marfan syndrome • 11 participants from non-treatment group crossed over to the treatment group • Average age at initial evaluation: 9.4 ± 5.3 years). Range 0.5-17.8 years • No treatment group: either none was recommended, or parental/participant refusal	• No significant difference in age, body size, BP, ocular, skeletal, cardiovascular abnormalities between male and female participants at baseline • Aortic root dilatation was present in 79% of participants at initial evaluation • Treated (beta-blocker and calcium channel blocker) participants had slower aortic growth than untreated participants • Major cardiovascular complications developed in 5 participants despite long-term pharmacologic therapy: mitral regurgitation and aortic regurgitation, distal aortic dissection, and cardiovascular surgery	• The study reports a beneficial impact of drug therapy on the absolute and relative rates of aortic root growth in children with Marfan syndrome • The study authors report however, all aortic complications occurred in participants on long-term therapy and therefore improved survival may be more fundamentally related to improved detection and appropriately timed surgical intervention.

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Table 4. Additional retrospective and prospective studies evaluating beta-blocker therapy versus no treatment *(Continued)*

Salim 1994	• Retrospective, non-randomised study comparing beta-blocker (N = 100) vs no treatment (N = 13) • Beta-blocker dose was achieved on basis of exercise challenge • Beta blockers: propranolol and atenolol • Aortic root diameter measured by Echocardiogram, CT or MRI • Follow-up: approximate range: 2-8 years	• 113 participants at 2 centres • Control group: those who couldn't or wouldn't take beta-blocker therapy • Age < 21 years at initial visit • Mean age (years): control 10.2 ± 4.6, treatment: 14.1 ± 3.4 in 1 centre, 10.4 ± 3.4 in the other centre • Heart rate and BP were used as measures of dosing and treatment efficacy	• Mean aortic root diameter ≥ 95th percentile for the normal population • Mean aortic root diameter was similar among groups at baseline • Mean aortic diameter was significantly larger in the control group • 5 participants from the treated group required aortic valve replacement. • Initial and final aortic root diameters in the surgical-treated group was significantly larger than in remaining participants in the treated group • Rapid increase in aortic root diameter during prepubertal and early pubertal years with maximal rate of increase during years 6-14	• Greatest rate of aortic root dilatation was observed in the group that didn't receive any therapy • The study authors recommend that participants with Marfan syndrome should begin beta-blocker at the earliest age possible with the dose titrated to the largest dose tolerated.
Selamet Tierney 2007	• Retrospective, multicentre study evaluating the rate of aortic dilatation in children with Marfan syndrome prescribed beta-blockade therapy (N = 29) compared to no treatment (N = 34) • Atenolol dose titrated to goal dose of 25 mg in children, 50 mg in adolescents • Aortic diameters were measured by echocardiography at 18-month to 3-year intervals • Follow-up: 81 months in control group, 76 months in treated group	• 63 participants with Marfan syndrome from 2 centres • Age: ≤ 18 years • Mean age: control v treatment: 9.2 v 8.8 years • Baseline: both groups well matched for mean age, weight, height, body surface area, sex, heart rate and heart rate z-score	• No significant difference in aortic root measurements at baseline or study end between the treatment and control groups. • 1 death in total from the control group: died peri-operatively during aortic valve replacement • 3 participants in total underwent aortic root replacement: 1 participant in the treatment group had intervention after aortic dissection. 2 control participants underwent elective intervention) • Side effects documented in 35% of the treatment group • Similar symptoms reported in 21% of the untreated group • Specific exercise testing to assess adequacy of beta-blockade not routinely performed, but heart rate and heart rate z-scores were lower in the treatment group.	• Beta-blocker therapy does not significantly alter the rate of aortic root dilatation in children with Marfan syndrome. • Similar number of participants from both study groups reached clinical endpoints • The authors recommend that life-time beta-blocker therapy during childhood be reconsidered given their study findings, the potential for side effects and the lack of favourable late outcome data.
Silverman 1995	• Large retrospective study with primary goal to evaluate life-expectancy in Marfan syndrome	• 419 participants with Marfan syn-	• Mean age for living members of the treated group was 33 ± 14 years compared to 31 ± 17 years in	• Life expectancy for participants increased by > 25%, due to an overall improved population life

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Table 4. Additional retrospective and prospective studies evaluating beta-blocker therapy versus no treatment *(Continued)*

	• Beta-blockers: propranolol, atenolol, metoprolol and nadolol	drome from 4 centres • 119 participants were on beta-blocker therapy • Mean age when beta-blockade therapy was begun: 28 ± 14 years	those who had never received beta blockers (P = 0.29) • Median cumulate probability in beta-blocker group was 72 years, compared to 70 years with no treatment (P = 0.01) • Of the 47 participants that died, 8 were taking beta-blockers.	expectancy, benefits of cardiovascular surgery, and increased frequency of diagnosis. • Study authors state that their study design doesn't permit direct assessment of beta-blockade on survival, however, their data suggest that medical therapy with beta-blocker confers benefit in survival.
Tahernia 1993	• Prospective study assessing beta-blocker therapy versus no treatment in 6 people with Marfan syndrome • Aortic dimensions measured by echocardiography annually • Propranolol 15 mg twice a day • Follow-up: 2-5 years	• 6 participants (3 on propranolol, 3 controls) • Mean age at beginning of study: 10 years in the study group, 9 years in the control group	• Control group had mild-moderate aortic dilatation, treatment group had moderate-severe aortic dilatation • 3 participants on beta-blocker: no further dilatation of the aortic annulus diameter and ascending aorta. No side effects were reported • 3 participants on no treatment: evidence of progressive dilatation	• After 2-5 years of follow-up, no progressive aortic dilatation was seen in any of the participants receiving low-dose beta-blockers

ACEI: angiotensin-converting enzyme inhibitor; AGV: aortic growth velocity; BP: blood pressure; CT: computerised tomography; MRI: magnetic resonance imaging

Table 5. Additional retrospective and prospective studies evaluating beta-blocker therapy versus other antihypertensive treatment

Study	Study design	Patient population	Results	Conclusions
Bhatt 2015	• Randomised, double-blind, parallel trial of losartan vs atenolol comparing their effects on arterial stiffness and left ventricular function in adults with Marfan syndrome • Losartan 100 mg 1/day • Atenolol 50 mg 1/day • Follow-up: 6 months	• 34 participants • Age: > 18 years • Atenolol; N = 17 • Losartan; N = 17 • Mean age in losartan group: 36 years, atenolol group: 34 years	• 2 study groups were similar in all pre-treatment variables (age, gender, heart rate, BP, cardiac and aortic measurements) • Atenolol decreased pulse wave velocity significantly compared to losartan. However, this improvement was attenuated when adjusted for change in heart rate. • Losartan decreased central augmentation pressure significantly compared to atenolol • No significant change in aortic root or ascending aortic diameter between the 2 study groups	• Both atenolol and losartan favourably affected aortic stiffness in adults with Marfan syndrome • Different mechanisms on improving aortic functional properties are implicated • Study authors suggest a role for both be-

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Table 5. Additional retrospective and prospective studies evaluating beta-blocker therapy versus other antihypertensive treatment *(Continued)*

				ta-blockers and ARBs in the treatment of Marfan syndrome.
Forteza 2016	• Phase IIIb, randomised, parallel, double-blind study to determine the efficacy of losartan (N = 70) or atenolol (N = 70) in Marfan syndrome • Follow-up: 3 years	• 140 participants from 2 clinical centres • Mean age: range 5-60 years • Inclusion criteria: aortic root diameter < 45 mm	• No serious drug-related adverse effects observed • Aortic root diameter increased significantly in both groups	• There was no significant difference in progression of aortic root and ascending aortic diameters between losartan and atenolol in participants with Marfan syndrome
Lacro 2014	• Randomised, multicentre trial comparing losartan (N = 305) with atenolol (N = 303) in children and young adults with Marfan syndrome • Atenolol was increased on the basis of haemodynamic response to a maximum dose of 4 mg/kg daily • Losartan was adjusted on the basis of body weight to a maximum dose of 1.4 mg/kg daily • Aortic measurements performed by echocardiography every study visit, 6-12 months apart • Follow-up: 3 years	• 604 participants from 21 clinical centres • Mean age: 11.5 in atenolol group, 11.0 in losartan. Range: 6 months-25 years • Aortic-root z-score was > 3.0 in both groups	• Similar baseline clinical and echocardiographic characteristic between groups • There was no significant difference in baseline-adjusted rate of change in aortic-root z-score between the 2 study groups • Small but significant difference in favour of atenolol in absolute diameter and z-score for aortic annulus • Both study groups indicated a decrease in the degree of aortic-root dilatation relative to body-surface area • Younger age at baseline was associated with greater decrease in aortic-root z-score over time in both groups • Diastolic BP was slightly lower in the atenolol group, but there were no differences in systolic or mean BPs • Heart rate was significantly lower in the atenolol group • There was no significant difference in 3 years in the rates of adverse clinical outcomes (aortic root surgery, aortic dissection, death) • Rate of adverse events possibly higher in atenolol group, but no significant difference in serious adverse events • No significant difference in withdrawal rate (11% per group) or median time to withdrawal.	• No significant difference in the rate of aortic root dilatation between the losartan and beta-blocker therapy group among children and young adults with Marfan syndrome
Sandor 2015	• Randomised, double-blind. pilot study assessing the effects of losartan v atenolol on the	• All 17 eligible partici-	• Baseline height, weight, body surface area, body mass and BP were similar. There was a significant gender difference.	• Study authors cannot draw defi-

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Table 5. Additional retrospective and prospective studies evaluating beta-blocker therapy versus other anti-hypertensive treatment *(Continued)*

	biophysical properties of the aorta in Marfan and Loeys-Dietz syndromes (LDS) • Atenolol: 25 mg-50 mg, losartan 25 mg daily • Aortic dimensions measured by echocardiography prior to and after therapy • Follow-up: 12 months	pants were diagnosed with Marfan syndrome, 1 tested positive for both Marfan syndrome and LDS • Atenolol group: 9 women • Losartan group: 7 men, 1 woman	• No significant aortic root dilatations occurred during the trial. • There was no significant difference for losartan to decrease pulse wave velocity and stiffness index • There was no significant difference for atenolol to improve hydraulic power • There was no decrease in contractility by atenolol • Adverse effects were not reported	nite conclusions due to limitations of the study, but suggest atenolol and losartan have different mechanisms of action on vascular function
Williams 2012	• Randomised, double-blind cross-over trial assessing the effects of atenolol, perindopril and verapamil on haemodynamic and vascular function in Marfan syndrome • Atenolol: 75 mg • Perindopril 4 mg • Verapamil 240 mg • Echocardiographic measurements • Follow-up: 18 weeks	• 18 participants from 2 tertiary congenital heart disease centres • Mean age: 30.4 ± 11.7	• Aortic root dimensions < 5 cm at study baseline • All drug groups reduced central systolic BP and brachial pressure. • Atenolol reduced heart rate and delayed aortic wave travel • No-drug group altered the pulse wave velocity • No significant change in aortic root diameter between groups and between baseline and study endpoint	• All drug groups reduced peripheral and central systolic BP • Study authors suggest beta-blockers have a continuing role in the treatment of Marfan syndrome
Yetman 2005	• Prospective, non-randomised trial assessing the effects of enalapril vs beta-blocker therapy in people with Marfan syndrome • Beta-blocker: propranolol or atenolol depending on participant weight. Dose titrated to maximum of 2 mg/kg daily for atenolol, 1 mg/kg twice daily for propranolol • ACEI: enalapril. Titrated to maximum dose of 10 mg twice daily • Doses adjusted according to adverse effects experienced by participant, not haemodynamic effects	• 57 participants: 32 enalapril, 24 atenolol, 2 propranolol • Mean age at start of therapy (years): 12.8 ± 7.8	• Improved aortic distensibility and a reduced aortic stiffness index in participants receiving enalapril and subsequently associated with a slower rate of aortic growth • 6 participants from beta-blocker group discontinued treatment due to adverse effects (depression, fatigue, short-term memory loss), and subsequently enrolled to enalapril group • 1 death from beta-blocker treatment group (documented ventricular tachyarrhythmia); no evidence of aortic dissection • 9 participants had aortic root replacement (2 from enalapril, 7 from the beta-blocker group)	• ACEI provide therapeutic benefit in adults with Marfan syndrome compared to beta-blocker treatment

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Table 5. Additional retrospective and prospective studies evaluating beta-blocker therapy versus other anti-hypertensive treatment *(Continued)*

- Bi-annual echo-cardiographic assessment
- Follow-up: 3.0 ± 0.2 years

ACEI: ACEI: angiotensin-converting enzyme inhibitor; ARB: angiotensin receptor blockers; BP: blood pressure

APPENDICES

Appendix 1. Search Strategies

CENTRAL

#1 MeSH descriptor: [Marfan Syndrome] this term only

#2 marfan* next syndrom*

#3 MeSH descriptor: [Arachnodactyly] this term only

#4 arachnodactyl*

#5 MeSH descriptor: [Mitral Valve Prolapse] this term only

#6 mitral valve* near/2 (flop* or prolapse*)

#7 MeSH descriptor: [Aortic Aneurysm] this term only

#8 aort* next (aneur?sm* or dilat* or dissect*)

#9 #1 or #2 or #3 or #4 or #5 or #6 or #7 or #8

#10 MeSH descriptor: [Adrenergic beta-Antagonists] explode all trees

#11 betablocker*

#12 beta* near/3 block*

#13 beta and (adrenergic near/6 block*)

#14 acebutolol

#15 atenolol

#16 alprenolol

#17 betaxolol

#18 bisoprolol

#19 bupranolol

#20 butoxamine

#21 carvedilol

#22 carteolol

#23 celiprolol

#24 esmolol

#25 dihydroalprenolol

#26 labetalol

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#27 levobunolol

#28 metipranolol

#29 metoprolol

#30 nadolol

#31 oxprenolol

#32 penbutolol

#33 pindolol

#34 practolol

#35 propranolol

#36 sotalol

#37 timolol

#38 adrenergic next beta*

#39 iodocyanopindolol

#40 sectral

#41 tenormin

#42 tenoretic

#43 kerlone

#44 zebeta

#45 ziac

#46 cartrol

#47 coreg

#48 brevibloc

#49 normodyne

#50 trandate

#51 lopressor

#52 toprol

#53 corgard

#54 penbutolol

#55 levatol

#56 visken

#57 inderal

#58 inderide

#59 innopran

#60 #10 or #11 or 12 or #13 or #14 or #15 or #16 or #17 or #18 or #19 or #20 or #21 or #22 or #23 or #24 or #25 or #26 or #27 or #28 or #29 or #30 or #31 or #32 or #33 or #34 or #35 or #36 or #37 or #38 or #39 or #40 or #41 or #42 or #43 or #44 or #45 or #46 or #47 or #48 or #49 or #50 or #51 or #52 or #53 or #54 or #55 or #56 or #57 or #58 or #59

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#61 #9 and #60

MEDLINE Ovid

1. Marfan Syndrome/

2. (marfan* adj syndrom*).tw.

3. Arachnodactyly/

4. arachnodactyl*.tw.

5. Mitral Valve Prolapse/

6. (mitral valve* adj2 (flop* or prolapse*)).tw.

7. Aortic Aneurysm/

8. (aort* adj (aneur?sm* or dilat* or dissect*)).tw.

9. or/1-8

10. exp Adrenergic beta-Antagonists/

11. betablocker*.tw.

12. (beta* adj3 block*).tw.

13. (beta and (adrenergic adj6 block*)).tw.

14. acebutolol.tw.

15. atenolol.tw.

16. alprenolol.tw.

17. betaxolol.tw.

18. bisoprolol.tw.

19. bupranolol.tw.

20. butoxamine.tw.

21. carvedilol.tw.

22. carteolol.tw.

23. celiprolol.tw.

24. esmolol.tw.

25. dihydroalprenolol.tw.

26. labetalol.tw.

27. levobunolol.tw.

28. metipranolol.tw.

29. metoprolol.tw.

30. nadolol.tw.

31. oxprenolol.tw.

32. penbutolol.tw.

33. pindolol.tw.

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34. practolol.tw.

35. propranolol.tw.

36. sotalol.tw.

37. timolol.tw.

38. (adrenergic adj beta*).tw.

39. iodocyanopindolol.tw.

40. sectral.tw.

41. tenormin.tw.

42. tenoretic.tw.

43. kerlone.tw.

44. zebeta.tw.

45. ziac.tw.

46. cartrol.tw.

47. coreg.tw.

48. brevibloc.tw.

49. normodyne.tw.

50. trandate.tw.

51. lopressor.tw.

52. toprol.tw.

53. corgard.tw.

54. penbutolol.tw.

55. levatol.tw.

56. visken.tw.

57. inderal.tw.

58. inderide.tw.

59. innopran.tw.

60. or/10-59

61. 9 and 60

62. randomized controlled trial.pt.

63. controlled clinical trial.pt.

64. randomized.ab.

65. placebo.ab.

66. drug therapy.fs.

67. randomly.ab.

68. trial.ab.

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69. groups.ab.

70. 62 or 63 or 64 or 65 or 66 or 67 or 68 or 69

71. exp animals/ not humans.sh.

72. 70 not 71

73. 61 and 72

74. adverse effects.fs.

75. contraindications.fs.

76. poisoning.fs.

77. toxicity.fs.

78. drug effects.fs.

79. (toxi* adj2 (effect or effects or reaction* or event or events or outcome*)).tw.

80. (adverse* adj2 (effect or effects or reaction* or event or events or outcome*)).tw.

81. (side adj3 (effect or effects)).tw.

82. (adr or adrs).tw.

83. or/74-82

84. exp animals/ not humans.sh.

85. 83 not 84

86. 61 and 85

87. 73 or 86

Embase Ovid

1. Marfan Syndrome/

2. (marfan* adj syndrom*).tw.

3. Arachnodactyly/

4. arachnodactyl*.tw.

5. Mitral Valve Prolapse/

6. (mitral valve* adj2 (flop* or prolapse*)).tw.

7. Aortic Aneurysm/

8. (aort* adj (aneur?sm* or dilat* or dissect*)).tw.

9. or/1-8

10. exp beta adrenergic receptor blocking agent/

11. betablocker*.tw.

12. (beta* adj3 block*).tw.

13. (beta and (adrenergic adj6 block*)).tw.

14. acebutolol.tw.

15. atenolol.tw.

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16. alprenolol.tw.

17. betaxolol.tw.

18. bisoprolol.tw.

19. bupranolol.tw.

20. butoxamine.tw.

21. carvedilol.tw.

22. carteolol.tw.

23. celiprolol.tw.

24. esmolol.tw.

25. dihydroalprenolol.tw.

26. labetalol.tw.

27. levobunolol.tw.

28. metipranolol.tw.

29. metoprolol.tw.

30. nadolol.tw.

31. oxprenolol.tw.

32. penbutolol.tw.

33. pindolol.tw.

34. practolol.tw.

35. propranolol.tw.

36. sotalol.tw.

37. timolol.tw.

38. (adrenergic adj beta*).tw.

39. iodocyanopindolol.tw.

40. sectral.tw.

41. tenormin.tw.

42. tenoretic.tw.

43. kerlone.tw.

44. zebeta.tw.

45. ziac.tw.

46. cartrol.tw.

47. coreg.tw.

48. brevibloc.tw.

49. normodyne.tw.

50. trandate.tw.

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51. lopressor.tw.

52. toprol.tw.

53. corgard.tw.

54. penbutolol.tw.

55. levatol.tw.

56. visken.tw.

57. inderal.tw.

58. inderide.tw.

59. innopran.tw.

60. or/10-59

61. 9 and 60

62. random$.tw.

63. factorial$.tw.

64. crossover$.tw.

65. cross over$.tw.

66. cross-over$.tw.

67. placebo$.tw.

68. (doubl$ adj blind$).tw.

69. (singl$ adj blind$).tw.

70. assign$.tw.

71. allocat$.tw.

72. volunteer$.tw.

73. crossover procedure/

74. double blind procedure/

75. randomized controlled trial/

76. single blind procedure/

77. 62 or 63 or 64 or 65 or 66 or 67 or 68 or 69 or 70 or 71 or 72 or 73 or 74 or 75 or 76

78. (animal/ or nonhuman/) not human/

79. 77 not 78

80. ae.fs.

81. to.fs.

82. co.fs.

83. si.fs.

84. (toxi* adj2 (effect or effects or reaction* or event or events or outcome*)).tw.

85. (adverse* adj2 (effect or effects or reaction* or event or events or outcome*)).tw.

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86. (side adj3 (effect or effects)).tw.

87. (adr or adrs).tw.

88. adverse drug reaction/

89. or/80-88

90. (animal/ or nonhuman/) not human/

91. 89 not 90

92. 61 and 79

93. 61 and 91

94. 92 or 93

Science Citation Index Expanded and the Conference Proceeding Citation Index –Science on Web of Science Core Collection

#19 #18 AND #17

#18 TOPIC: ((random* or blind* or allocat* or assign* or trial* or placebo* or crossover* or cross-over*))

#17 #16 AND #5

#16 #15 OR #14 OR #13 OR #12 OR #11 OR #10 OR #9 OR #8 OR #7 OR #6

#15 TOPIC: (lopressor or toprol or corgard or penbutolol or levatol or visken or inderal or inderide or innopran)

#14 TOPIC: (kerlone or zebeta or ziac or cartrol or coreg or brevibloc or normodyne or trandate)

#13 TOPIC: (propranolol or sotalol or timolol or "adrenergic beta*" or iodocyanopindolol or sectral or tenormin or tenoretic)

#12 TOPIC: (labetalol or levobunolol or metipranolol or metoprolol or nadolol or oxprenolol or penbutolol or pindolol or practolol)

#11 TOPIC: (alprenolol or betaxolol or bisoprolol or bupranolol or butoxamine or carvedilol or carteolol or celiprolol or esmolol or dihydroalprenolol)

#10 TOPIC: (atenolol)

#9 TOPIC: (acebutolol)

#8 TOPIC: ((beta same (adrenergic near/6 block)))

#7 TOPIC: ((beta* near/3 block*))

#6 TOPIC: (betablocker*)

#5 #4 OR #3 OR #2 OR #1

#4 TOPIC: (("aort* aneur?sm*" or "aort* dilat*" or "aort* dissect*"))

#3 TS=(("mitral valve*" near/2 (flop* or prolapse*)))

#2 TOPIC: (arachnodactyl*)

#1 TOPIC: ((marfan* syndrom*))

Appendix 2. Data Extraction form

Beta-blockers for preventing aortic dissection in Marfan's syndrome

Data Extraction form

Name of reviewer: _____

Date of data collection: _____

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1. General information

	Description in report	Location in text (page/figure/table)
Study title		
Authors		
Study dates (total duration)		
Date of publication		
Journal name		
Study location (country/city)		
No. and location of study centres		
Study settings (e.g. hospital/clinic/community)		
Additional notes		

2. Study eligibility

	Description in report	Location in text (page/figure/table)
Study design/type		
Study objective		
Study duration > 1 year	Yes ☐ No ☐ Unclear ☐	
Intervention: Beta-blocker monotherapy?	Yes ☐ No ☐ Unclear ☐	
Participants have diagnosis of Marfan's Syndrome	Yes ☐ No ☐ Unclear ☐	
Does the study meet the criteria for inclusion?	Yes ☐ No ☐ Unclear ☐	
Additional notes		

3. Methods

	Description in report	Location in text (page/figure/table)
Study protocol available?	Yes ☐ No ☐ Unclear ☐	

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(Continued)

Ethical approval obtained	Yes ☐ No ☐ Unclear ☐
Run-in period	
Method of recruitment	
Method of randomisation	
Unit of allocation (individuals or groups)	
Duration of participation	
Additional notes	

4. Participants

	Description in report	**Location in text (page/figure/table)**
Number of participants randomised		
Number of participants analyzed		
Diagnostic criteria for Marfan's syndrome		
Inclusion criteria		
Exclusion criteria		
Age range and mean		
Sex ratio		
Other sociodemographics		
Co-morbidities		
Subgroups measured		
Baseline imbalances		
Number lost to follow-up or withdrawn		
Additional notes		

5. Interventions

	Description in report	**Location in text (page/figure/table)**

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(Continued)

Intervention (name of beta-blocker)
Dose
Route
Frequency
Duration
Number of participants assigned to intervention group
Comparison
Dose
Route
Frequency
Duration
Number of participants assigned to comparison group
Additional notes

6. Outcomes

	Description in report	Location in text (page/figure/table)
Primary outcomes		
Method of measuring primary outcomes		
Secondary outcomes		
Method of measuring secondary outcomes		
Follow-up time line (frequency and total duration)		
Investigators/assessors		
Additional notes		

7. Results ***(copy and paste for each outcome)***

	Description in report	Location in text (page/figure/table)

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(Continued)

Outcome		
Follow-up Timepoint (s)		
Results	Intervention group	Comparison group
Subgroup analysis performed?		
Baseline data	Intervention group	Comparison group
No. of participants followed to the end of study		
No. of participants missing/removed (give reasons)		
Unit of analysis		
Statistical method used		
Additional notes		

8. Risk of Bias assessment

	Risk of bias (Low/high/unclear)	**Support for judgement (Description in report)**	**Location in text (page/figure/table)**
Random sequence generation *(selection bias)*			
Allocation concealment *(selection bias)*			
Blinding of participants and personnel *(performance bias)*			
Blinding of outcome assessment *(detection bias)*			
Incomplete outcome data *(attrition bias)*			
Selective reporting *(reporting bias)*			
Other bias			
Additional notes			

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9. Additional information/comments

	Description in report	Location in text (page/figure/table)
Funding sources and role of funders		
Possible conflicts of interest		
Additional information required (contact authors)		
Correspondence received		
Additional notes		

CONTRIBUTIONS OF AUTHORS

HK and VM formulated the idea for review, registered the review title and developed the basis of the protocol.

HK wrote the protocol with contributions from VM and KL.

HK and KL screened citations resulting from search findings and determined trials meeting inclusion/exclusion criteria and assessing risk of bias.

HK and VM extracted data and performed analyses.

All authors contributed to writing the completed review.

DECLARATIONS OF INTEREST

HK: none known
KL: none known
VM: none known

SOURCES OF SUPPORT

Internal sources

- Department of Anesthesiology, Pharmacology & Therapeutics, University of British Columbia, Canada.

External sources

- No sources of support supplied

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

Although not stated in the protocol, we have included a 'Summary of findings' table listing all important clinically relevant outcomes in the review. The included study provided little information on clinically relevant outcomes, however, contacting study authors significantly improved reporting of methodology, assessing risk of bias and obtaining additional information regarding individual non-fatal morbidity outcomes. To provide clinically useful information to physicians and policy makers we decided to include them in the 'Summary of findings' table and the Data and analysis section.

Although stated in the protocol, we did not perform a search of relevant manufacturers' websites for trial information due to lack of resources.

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INDEX TERMS

Medical Subject Headings (MeSH)

Adrenergic beta-Antagonists [*therapeutic use]; Aneurysm, Dissecting [etiology] [mortality] [*prevention & control]; Marfan Syndrome [*complications]; Propranolol [*therapeutic use]

MeSH check words

Adolescent; Adult; Humans; Middle Aged; Young Adult

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